A STUDY ON PLASMA FIBRINOGEN AS A RISK FACTOR FOR ISCHAEMIC STROKE

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CERTIFICATE

This is to certify that this dissertation entitled **"A STUDY ON PLASMA FIBRINOGEN AS A RISK FACTOR FOR ISCHAEMIC STROKE"** submitted by Dr. M. THANGARAJ to The Tamil Nadu Dr.M.G.R. Medical University, Chennai is in partial fulfillment of the requirement for the award of M.D. degree Branch I (General Medicine) and is a bonafide research work carried out by him under direct supervision and guidance.

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DECLARATION

I **Dr. M. THANGARAJ** declare that I carried out this work on **"A STUDY ON PLASMA FIBRINOGEN AS A RISK FACTOR FOR ISCHAEMIC STROKE"** at Department of General Medicine, Government Rajaji Hospital during the period of August 2005 – July 2006. I also declare that this bonafide work or a part of this work was not submitted by me or any other for any award, degree, diploma to any university, board either in India or abroad.

This is submitted to the Tamilnadu Dr.M.G.R. Medical University, Chennai in partial fulfillment of the rules and regulation for the M.D. Degree examination in General Medicine.

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CONTENTS

INTRODUCTION

Stroke is one of the major public health problem in all over the world. It plays an important role in the morbidity and mortality in the late middle age and in the elderly. Stroke after heart disease and cancer is the most common cause of death.

Among the neurologic disease of adult life the cerebrovascular disease clearly rank first in frequency and importance. At least Fifty percent of the neurologic disorders in a general Hospital are of this type[1].

The burden of stroke is likely to increase substantially in the future because of the aging population. Apart from implementing effective stroke prevention programs identification of risk factors associated with stroke may help to ease the burden of this epidemic.

Stroke is a heterogenous disease. Ischaemic and haemorrhagic strokes are the two major types of stroke with different pathogenesis and outcome.

This study attempts to identify the significance of plasma Fibrinogen as a risk factor for stroke and also to study the correlation between the plasma fibrinogen levels and other major risk factors for stroke.

AIM OF THE STUDY

- To study correlation between high plasma Fibrinogen and ischaemic stroke.
- To study the correlation between high plasma Fibrinogen in cerebrovascular disease with special reference to age, sex, smoking. Hypertension, Diabetes mellitus and obesity.
- To compare the results with age and sex matched control population.

REVIEW OF LITERATURE

INTRODUCTION

Stroke is a clinical syndrome characterized by acute loss of focal brain or monocular function with symptoms lasting greater than 24 hours and which is thought to be due to inadequate cerebral or ocular blood supply.

The clinical manifestations of stroke are highly variable because of the complex anatomy of the brain and its vasculature. About 80% of all stroke are ischaemic 10% are due to primary intracerebral haemorrhage and 5% are due to subarachnoid hemorrhage in the community.

Cerebrovascular disease most commonly present as an acute focal stroke. Ischaemic arterial disease may present, particularly in elderly with a gradual decline in intellectual function with or without sensorymotor limb deficit or gait disorder. Haemorrhage from the major cerebral arteries of the circle of willis in to the subrachnoid space.

Cerebral ischaemia is caused by a reduction in blood flow that lasts longer than several seconds Neurologic symptoms are manifest with in seconds because neurons lack glycogen, so energy failure is rapid. A fall in cererbral blood flow to zero cause infarction within 4 to 10min, and less than 16 to 18ml/100g tissue per min cause infarction within an hour, and blood supply <20ml /100g per min cause ischaemia without infarction unless prolonged for

several hours or days. If blood flow is quickly restored brain tissue can recover fully and patients symptoms are only transient; this is defined as transient ischaemic attack. Typically the neurologic signs and symptoms of a TIA last for 5 to 15 mnts. But by definition must last for <24 hours. Stroke has occurred when the signs and symptoms last for >24hours. Focal ischaemia or infarction is usually caused by thrombosis of the cerebral vessels or by emboli from a proximal artery or heart. Cerebral haemorrhage produces neurologic symptoms by producing a mass effect on neural structures or from the toxic effects of blood itself.

BLOOD SUPPLY TO THE BRAIN:

The brain receives 20% of cardiac output, but comprises only 2% of total body weight. This rich blood supply is delivered by the two internal carotid and two vertebral arteries, which anastamose at the base of the brain to form the circle of Willis[4]. The carotid arteries supply the anterior portions of brain and the vertebro basilar arterial system supply the posterior portions of the brain.

CAROTID ARTERIAL SYSTEM:

The left common carotid artery arises directly from the aorta and right common carotid from the innominate artery. The internal carotid artery starts at the carotid sinus at the bifurcation of the common carotid artery. It runs up the neck without any branches to reach the base of the skull and enters the carotid

canal of the petrous bone. It then runs through the cavernous sinus in S shaped curve, pierces the dura and bifurcates into anterior and middle cerebral artery.

BRANCHES OF INTERNAL CAROTID ARTERY

OPHTHALMIC ARTERY:

The ophthalmic artery is the first major branch of the ICA and arises in the cavernous sinus. It passes through the optic foraman to supply the eye and other structures in the orbit.

POSTERIOR COMMUNICATING ARTERY:

This is the next artery to arise from the internal carotid artery. It passes back to join the first part of the posterior cerebral artery, so contributing to the circle of Willis.

ANTERIOR CHOROIDAL ARTERY:

It arises from the last section of internal carotid artery and supplies optic tract, internal capsule, parts of basal ganglia, thalamus and optic radiation.

ANTERIOR CEREBRAL ARTERY:

The anterior cerebral artery enters the interhemispheric fissure, anastomoses with its counter part of opposite side via anterior communicating artery, curves around the genu of corpus callosum and supplies the anterior and medial parts of the cerebral hemisphere.

MIDDLE CEREBRAL ARTERY

The middle cerebral artery enters the sylvian fissure and divides into 204 branches which supply the lateral parts of the cerebral hemisphere. from its main trunk a medial and lateral group of tiny lenticulostriate arteries pass upwards to penetrate the base of the brain and the supply the basal ganglia and internal capsule. The artery supplies the whole of the motor cortox except the leg area.

VERTEBRO BASILAR SYSTEM:

VERTIBRAL ARTERY:

The vertebral artery arises from the proximal subclavian artery and ascends to pass through the transverse foramina of the second to the sixth cervical vertebrae, giving off small muscular branches on the way. It passes posteriorly around the atlas and enters the skull through the foramen magnum. It unites with the opposite vertebral artery on the vertebral surface of the brain stem to form the basilar artery. The vertebral artery gives rise to anterior and posterior spinal arteries, the posterior inferior cerebellar arteries and small penetrating branches to the medulla[12].

BASILAR ARTERY

The basilar artery ascends ventral to the pons to the pontomidbrain junction in the inter peduncluar cistern where it divides into two posterior cerebral arteries. Numerous small branches are given to the brain stem and

cerebellum. it gives rise to the anterior inferior cerebellar artery and superior cerebellar artery.

POSTERIOR CEREBRAL ARTERY:

The posterior cerebral artery encircles the midbrain close to the oculomotor nerve at the level of tentorium and supplies the inferior part of the temporal lobe, and the occipital lobe. Many small branches supply the midbrain, thalamus, hypothalamus and geniculate bodies[19].

CIRCLE OF WILLIS:

The circle of Willis in the interpeduncular fossa at the base of the brain. It is formed by anastomosis between the two internal carotid arteries and the two vertebral arteries. The anterior communicating the anterior cerebral, internal carotid, posterior communicating, posterior cerebral and the basilar arteries all contribute to the circle. The circle of Willis allows blood that enters either by the internal carotid or the vertebral arteries to be distributed to any part of either cerebral hemisphere. The cortical and central branches arise from the circle and supply the brain substance.

ARTERIES TO SPECIFIC BRAIN AREAS

Mainly the medial and lateral striate central branch of the middle cerebral artery supply the corpus striatum and the internal capsule; the central branches of the anterior cerebral artery supply the remainder of the structures.

The posterior cerebral, posterior communication and basilar arteries supply the thalamus.

The posterior cerebral, superior cerebellar, and basilar arteries supply the mid brain.

The basilar and anterior, inferior and superior cerebellar arteries supply the pons.

The vertebral, anterior and posterior spinal, posterior inferior cerebellar and basilar arteries supply the medulla oblongata.

VEINS OF THE BRAIN

EXTERNAL CEREBRAL VEINS

The superior cerebral veins pass upward over the lateral surface of the cerebral hemisphere and empty into the superior sagittal sinus. The superficial middle cerebral veins drain the lateral surface of the cerebral hemisphere; it runs inferiorly in the lateral sulcus and empties into the cavernous sinus. The deep middle cerebral vein drains the insula and is joined by the anterior cerebral vein and striate veins to form the basilar vein. The basilar vein ultimately joins the great cerebral vein, which in turn drains into the straight sinus.

INTERNAL CEREBRAL VEINS:

There are two internal veins, and the union of the thalamo striate vein and the choroidal vein at the interventricular foramen forms them. These two veins form the great cerebral vein that drains into the straight sinus.

EPIDEMIOLOGY

INCIDENCE OF STROKE:

Stroke is world wide health problem. It makes an important contribution to morbidity mortality and disability in developed as well as developing countries[24].

The first population based study conducted in Vellore showed an incidence of 13/1,00,000 population per year. The second population based study was carried out as a part of WHO collaborative study in Rohtak, Haryana between 1971-74 revealed an annual incidence of 33/1,00,000 population per year. The incidence of stroke rapidly increases with age. About a quarter occur below the age 65 and about a half below the age of 75.

PREVALENCE OF STROKE:

According to the Vellore study, prevalence rate per 1 lakh population was 56.9 per 1 lakh. The prevalence in Eastern part of India was found to be 160-270 per 1 lakh[24].

MORTALITY

Stroke is one of the leading cause of death and disability throughout the world. The WHO collaborative study showed that both in developed and developing countries, nearly one third of the stroke patients died within 3 weeks and 48 percent died within one year[24].

RISK FACTORS FOR STROKE

AGE :

Age is the strongest risk factor for ischaemic stroke, primary intracerebral haemorrhage and subarachoid haemorrhage[3].

SEX:

Male are associated with increased risk of stroke.

BLOOD PRESSURE:

Increasing blood pressure is strongly associated with subsequent stroke risk with all the main pathological types[23]. Hypertension probably increases the stroke risk by increasing the extent and severity of atheroma and the prevalence of small vessel disease in the perforating arteries with in the brain. The treatment of hypertension reduces the risk of stroke.

CIGARETTE SMOKING:

Smoking is a strong risk factor for subarachnoid haemorrhage and for ischaemic stroke, but there is less association with primary intra cerebral haemorrhage. Smoking has been related to the extent of carotid disease in patients selected for angiography.

BLOOD LIPIDS:

The relationship between blood lipids and stroke is weaker than that for coronary artery disease, although studies have shown a relation between increases serum lipoprotein (a) and stroke[15].

DIABETES MELLITUS:

Diabetes mellitus increases the risk of cerebrovascular disease two to four fold compared with non diabetics[5]. Strokes secondary to diabetes mellitus may be caused by cerebrovascular atherosclerosis, cardiac embolism and rheological abnormalities. Strokes in diabetics are more likely to be fatal.

ATRIAL FIBRILLATION:

The most frequent potential cardiac source of embolism to the brain is atrial fibrillation, by virtue of clot forming in the left atrium. Both rheumatic and non rheumatic atrial fibrillation are associated with stroke. The risk of first stroke is about 5% per year in non rheumatic atrial fibrillation.

ALCOHOL:

Heavy alcohol consumption is an independent risk factor for haemorrhagic and ischaemic stroke. But modest alcohol consumption may be protective for ischaemic stroke[16]. Confusion arises because it is difficult to measure alcohol consumption.

EXERCISE:

Exercise reduced blood pressure, plasma cholesterol and fibrinogen and the risk of non insulin dependent diabetes mellitus. Lack of exercise is associated with increased incidence of stroke[7].

INFECTIONS AND INFLAMMATIONS:

There is evidence of an association between stroke and serum C-Reactive protein and various immediately proceeding and distant infections[8].

HOMOCYSTENIEMIA:

Heterozygotes for cystathionine synthetase deficiency have moderately raised levels of blood homocysteine with enough data linking these raised levels to coronary disease and stroke[23].

TRANSIENT ISCHAEMIC ATTACKS:

A patient with transient ischaemic attack has 5-10 times excess risk of getting a stroke than a person who does not.

CARDIOVASCULAR DISEASES:

Angina or Myocardial infarction is clearly associated with stroke, ECG abnormalities reflecting hypertension and coronary artery disease are risk factors for stroke. Rheumatic heart disease and cardiac failure are other risk factors. Claudication is a high risk factor for both stroke and myocardial infarction, presumably reflecting atheromatous disease in other parts of circulation.

CAROTID ARTERY DISEASE:

When carotid artery Stenosis is greater than 75% combined transient ischaemic attack and stroke rate is 10.5% per year[20].

PLASMA FIBRINOGEN:

Fibrinogen itself is a strong independent risk factor for coronary artery disease and stroke.

OTHER RISK FACTORS:

Abdominal obesity, snoring, corneal arcus, diagonal ear lobe crease, left ventricular hypertrophy are other risk factors.

CLASSIFICATION OF STROKE[12,25]:

Stroke can be classified in several ways

A) **Anatomic classification:**

I. By Vascular supply

a. Carotid

b. Vertebro basilar

II. By location

a. supra tentorial

- lobar
- Ganglionic/thalamic

b. Infratentorial

- Cerebellar
- Brainstem

B) PATHOPHYSIOLOGIC CLASSIFICATION

I **Ischaemic**

A) Thrombotic

- Lacunar Storke
- Large Vessels stroke

B) Embolic

- Cardioembolic
- Artery – artery embolic
- Cryptogenic
- Others

II Haemorrhagic

A) Intra parenchymal

B) Subarachnoid

CLINICAL FEATURES OF STROKE

TOTAL ANTEIROR CIRCULATION SYNDROME

A large haematoma in one cerebral hemisphere or an infarct large enough to affect the cortex[6], basal ganglia and internal capsule causes a characteristic clinical syndrome of

1. Contralateral hemiparesis with or without sensory deficit, involving the whole or at least two of three body areas (face, upper limb, lower limb)
2. A homonymous visual field defect and A new higher cerebral or cortical dysfunction (Dysphasia, neglect, visuospatial problems etc., depending on cerebral dominance). Often patients are so drowsy that any cognitive and visual field defect have to be assumed. A large haematoma may cause midline shift, transtentorial herniation and coma within 24 hours, whereas these changes take 2 or 3 days to evolve in infarct as cerebral edema develops.

PARTIAL ANTERIOR CIRCULATION SYNDROME

A lobar haemorrhage or cortical infarct causes a more restricted clinical syndrome consisting of only two of the three components of TACS[4], or just isolated cortical dysfunction such as dysphasia or a predominantly proprioceptive deficit in one limb. PACS are caused by occlusion of a branch of middle cerebral artery, usually as a consequence of embolism from heart or proximal arteries.

LACUNAR SYNDROME

The four main lacunar syndromes are :

1. Pure motor deficit: (about 50% of lacunar cases) is a unilateral motor deficit involving two of three areas (face, arm, leg). There are often sensory symptoms but no signs. The lesion is usually in internal capsule or pons[4].
2. Pure sensory stroke : (about 5%) has the same distribution as pure motor stroke but symptoms are sensory loss. The lesion is usually in thalamus.
3. Sensorimotor stroke (about 35%) lesion is usually in thalamus or internal capsule
4. Ataxic hemiparesis (about 10%) is a combination of corticospinal and ipsilateral cerebellar like dysfunction affecting arm / leg and includes the syndrome in which there is little more than dysarthria and one clumsy hand.

POSTERIOR CIRCULATION SYNDROME

Brainstem, cerebellar, thalamic or occipital lobe signs normally suggest infarction in region of vertebrobasilar circulation[4].

A combination of brain stem and occipital lobe signs is highly suggestive of infarction or thromboembolism of basilar artery.

THALAMIC STROKE:

Infarction or haemorrhage of thalamus is not common. It causes paralysis of upward gaze, small pupils, depressed consciousness, disorientation, aphasia, impairment of verbal memory.

CEREBELLAR STROKE:

They are uncommon. Extensive infarction or haemorrhage causes vertigo, nausea, horizontal nystagmus, ipsilateral and truncal ataxia, as well as dysarthria. There are often brain stem signs.

BOUNDARY ZONE INFARCTS:

These are infarcts in the border zones between arterial territories in the fronto parasagittal region (anterior boundary zone). They account for a small percentage of strokes. Systemic hypotension which is sudden and profound as during cardiac arrest may cause bilateral infarcts in posterior boundary zones[4].

DIAGNOSTIC EVALUATION OF STROKE:

The next step after clinical diagnosis of stroke is to differentiate whether the brain lesion is due to primary intra cerebral haemorrhage or cerebral infarction by CT scanning or MRI.

IMAGING THE BRAIN

ISCHAEMIC STROKE : The CT appearance of cerebral infarction is time dependent. Although the findings may be detected within 6-8 hours of onset, CT may be normal up to 24 hours.

Hyperacute infarct:

- normal in 50-60%
- hyperdense artery 25-50%
- obscuration of lentiform nuclei

Acute

- loss of grey white matter interfaces (insular ribbon sign, obscuration of cortico medullary white matter border)
- low density basal ganglia
- sulcal effacement

1-3 days

- increasing mass effect
- wedge shaped low density area that involves both grey and white matter
- haemorrhagic transformation may occur.

4-7 days

- gyral enhancement
- mass effect, edema persists

1-8 weeks

- contrast enhancement persists
- mass effect resolves

months to years

- encephalomalacic changes
- volume loss
- rarely calcification

As mentioned above early findings on CT may be sudden loss of grey white matter contrast and effacement of adjacent subarachnoid spaces. However by 24 hours the abnormal low attenuating area becomes obvious. Specifically insular ribbon sign has been defined as an early specific sign of MCA infarction. The early findings on non contrast CT are the result of development of cytotoxic edema. Occasionally CT scan through the suprasellar may show hyperintense MCA indicative of thrombus within the artery. Mass effect and decreased attenuation increases due to combination of cytotoxic and vasogenic edema. Mass effect from cytotoxic edema is maximum between 3-10 days, and may lead to herniation. Mass effect completely resolves by 3 weeks.

LACUNAR INFARCTION:

These are secondary to arterial disease affecting the deep penetrating vessels of brain. These arteries may demonstrate tiny foci of sclerosis caused by micro atheroma or lipohyalinosis. Because of the small size CT may miss the infarct.

MAGNETIC RESONANCE IMAGNING OF STROKE[4]:

Acute infarcts are identified more than and localized more distinctly on MRI as compared to CT. The earliest MRI findings are vascular flow related abnormalities. These include absence of normal flow void and slow flow with intravascular arterial enhancement. These signs can be detected with in minutes of symptom onset. Intravascular enhancement is seen nearly is there quarters of acute cortical infarct. Other early MRI findings include hyperintense signal on T2 weighted images, which may not be observed within 8 hours. On both initial and follow up examinations the TI weighted images are sensitive.

FIBRINOGEN

The two primary sequence of fibrinogen 340,000-Dalton molecule was completed and the primary structure was conceived as three pairs of polypeptide chains named A∝, Bβ, and ϒ, composed of 610, 461, and 411 amino acids, respectively. Each arm of the fibrinogen molecule contains single A∝, Bβ, and ϒ, chains from each of the three pairs of polypeptide chains.

The centeral domain is a dimeric structure in which each dimer contains the three amino terminals of the individual arms. The slightly thickened amino terminal ends of the Aα and Bβ chains represent fibrinopeptides A and B, respectively, which are not present in fibrin. The dimeric halves of the central domain are held together by three of 11 disulfide bonds, the rest of which are located between the Aα and Bβ chains and in the junctions between the central domain and the coiled-coils. These coiled-coils are composed of the single Aα and Bβ and γ chains supercoiled as α-helices. Six disulfide bonds in each coiled-coil are responsible for the supercoil structure and for the attachment to the central and lateral domains in the from of disulfide rings. The basic structure consists of three pairs of polypeptide chains: α, β and γ, arranged in a mirror image[9].

The amino acid residue orientation is such that the inside of the coiled-coil is hydrophobic and the outside is polar.

The lateral domains have a mass of 67, 200 Da each. Most of the bulk in each domain is represented by random folds of the γ and β lobes. There are four carbohydrate clusters, each 2,500 Da. Two are located on each lateral domain on the β chain and two on each arm in the γ chain, near the central domain. The Aα polar appendage, the site of primary cross-linking, is close to the carboxyl terminal of the γ chains.

Fibrinogen degradation by plasmin yielding key fibrinogen fragments is a physiologic process that normally takes place in vivo. However, this process can be reproduced in the laboratory. Plasmin digestion yields a set of core fragments, originally called fragments A, B, C, D and E. As determined by diethylaminoethyl chromatography, the fragments are labeled according to the order in which they emerge from the process. The intermediate products are fragment X and Y. the x fragment result from cleaving one of the coiled-coils midway between the central and lateral domain, yielding fragments D and Y. Future cleavage of fragment Y yields fragments D and E.

Plasma fibrinogen is synthesized exclusively by the hepatocyte, and the synthesis of the three chains is under the coordinated control of three separate gene localized on chromosome 4 Subsequent to assembly of the constituent polypeptide chain and the addition of carbohydrate side chains, the mature

molecule is secreted into the circulation. Where it manifests a half life of 4 days and a fractional catabolic rate of 25% day.

Fibrinogen plays a central role in three major functional processes.

1. The soluble fibrinogen molecule is converted into insoluble fibrin during the process of blood coagulation 2. The polymerized fibrin serves as a template for the localized assembly and activation of the fibrinolytic system, which modulates fibrin deposition and clot dissolution and 3. Fibrinogen binds to vascular cells such as platelets where it supports platelet aggregation and to endothelial cells, where it participates in tissue repair. The conversion of fibrinogen to insoluble fibrin can be divided into three distinct phases (1) Enzymatic cleavage of fibrinopeptides by thrombin. (2) Fibrin polymerization, and (3) Fibrin stabilization via covalent cross-linking by factor XIII a. in the first phases, thrombin cleaves the Arg 16 Gly 17 bond of the Aα chain and the Arg 14 gly 15 bond of the Bβ chain, resulting in the release of two molecule of fibrinopeptide A and two of fibrinopeptide B per molecule of fibrinogen, results in the formation of fibrin monomer, the constituent chains of which are now referred to as the α,β and γ chains. Although the proteolytic cleavage of FP-A and FP-B by thrombin appears to be simultaneous, the cleavage of FP-B does not lead to fibrin formation under physiologic condition. The association of thrombin with fibrinogen is in part mediated through its catalytic site, as shown by nuclear magnetic resonance and x-ray crystallographic studies of thrombin

bound to a discrete segment of the N-terminal of the Aα chain. However, thrombin also binds to fibrin through a noncatalytic site called the fibrinogen recognition site, which binds to a locus formed by the N- terminus of the β chain.

In intact fibrinogen, the negatively charged fibrinopeptides play a role in maintaining the dispersion of individual fibrinogen molecules, because subsequent, to their cleavage by thrombin the resulting fibrin monomers polymerize spontaneously. The polymerization process involves the reciprocal non-covalent interaction of molecular determinants in the frequent, E region of an adjacent fibrin monomer. The resulting dimer, which is arranged in a half-staggered overlap, continues to grow in length by the staggered addition of fibrin monomers, resulting in the formation of two-stranded, half staggered polymer referred to as a protofibril the basic structure unit of the fibrin clot. The final stage of fibrin formation is characterized by the factor XIII a mediated formation of covalent amide bonds between the E-amino groups specific lysine residues and γ $CONH_2$ groups of certain glutamine residues. These covalent bonds are first formed at the DD contact between the γ chains of two molecules. The dimerization of the γ chain formed by bridges between lys 406 of one γ chain and glu 398/399 of another is then followed by progressive covalent cross-linking of multiple-chains. Cross linking at branch points also produces D

trimers (or) D-tetramers. As a result of this covalent to both mechanical disruption and dissolution by plasmin.

In addition to plasma fibrinogen, the circulating blood contains a very small pool of fibrinogen, which is present with in the platelet α granules. Some have shown that the fibrinogen is synthesized by the megakaryocyte, but more investigations demonstrated that both megakaryocyte and platelets are capable of internalizing fibrinogen from plasma via a process mediated by glycoprotein II b/III a. platelet fibrinogen lacks γ chain. The discrepancy between the molecular and functional properties of plasma and platelet fibrinogen is depend on the ability of the platelet megakaryocyte to internalize the abnormal fibrinogen. Platelet fibrinogen is secreted after stimulation and plays a role in supporting haemostasis.

HYPERFINRINOGENEMIA

Plasma fibrinogen levels increase significantly with age, with life style habits such as smoking, and in certain pathologic conditions such as hypertension, obesity, and diabetes mellitus. However even, among normal individuals the plasma fibrinogen concentration varies and, although the exact regulatory mechanism is unknown, recent studies indicate that fibrinogen levels may be genetically controlled. For example high plasma fibrinogen concentrations have been observed in normal individuals exhibiting a special nucleotide sequence polymorphism at the 5’ untranslated region of the Bβchain

seems to be a rate limiting step in fibrnogen biosynthesis, increased trancription of this gene is likely to result in present in only a minority of the population. By contrast, in most individuals fibrinogen behaves as an acute phase reactant protein. Therefore its concentration is sensitive to inflammatory responses. In this process the release of IL – 6 by macrophages leads to an increase in transcription of Bβ gene, resulting in elevated levels of fibrinogen. It is also possible that a genetic polymorphism distinct from that in the 5' untranslated region described above and located within the IL-6 responsive element may play an important role in setting the level of fibrinogen in different individuals.

The concentration of plasma fibrinogen has important clinical implication, as indicated by several studies demonstrating that hyperfibrinogenemia is an independent risk factor in stroke and in IHD. Plasma fibrinogen concentration in the upperthird of the population increased the risk of CVD threefold as compared with those in the lower of fibrinogen such as 1 standard deviation (SD) (0.6 mg/ml) above the mean markedly increase the risk of CVD. When other risk factors for CVD stroke such as high BP, serum cholesterol, age, diabetes, and smoking were considered, high levels of fibrinogen were still evident as an important risk factor.

Plasma fibrinogen has been implicated in atherogenesis and in arterial thrombus formation. A number of epidemiologic studies have shown a

substantial and significant impact of fibrinogen on cardiovascular disease incidence including stroke.

Level of fibrinogen measured at the10th biannual examination in formation was also significantly related to incidence of vascular disease including stroke.

Fibrinogen was also positively associated with most of the major risk factors for stroke including age, hypertension, obesity and diabetes. There of fibrinogen and other clotting factors will yield important clues into the pathogenesis of atherosclerotic vascular disease.

Pai Mahes C, Chandrasekhara P. et al done a study to identify the significance of plasma fibrinogen as a risk factor for ischaemic stroke and also to study the correlation between plasma fibrinogen levels and other major risk factor to stroke. This study includes fifty patients with features of cerebrovascular accident., proved to have cerebral infarction. CT scan were taken for all cases were compared with fifty controls with respect to age and sex. Plasma fibrinogen was estimated in all cases and controls. This study shows significant statistical difference in cases and controls. Fibrinogen was high among the males and increases with age. It was significantly higher in diabetics when compared to non diabetics. It was also higher in hypertensive and smokers. Hyperfibrinogenemia is associated with stroke recurrence and TIA[21].

Lee , Lowe GD, M wood word Et all provides the relations of plasma fibrinogen to family History of premature heart disease, personal History of hypertension, diabetes, stroke and coronary heart disease. This large populations study found that plasma fibrinogen is not only a risk factor for coronary heart disease and stroke but it is also raised with family history of premature heart disease and with personel history of hypertension diabetes and obesity[18].

Aizhong gu and K. Sree Kumarannair found the association between atherosclerotic disease and fibrinogen levels, plasma concentrations of fibrinogen increased with age. This study also demonstrated that the increased levels of fibrinogen represent a slower rate of disposal of fibrinogen rather than increased production rate[2].

Graziella Bruno, et al studied the distribution of plasma fibrinogen levels and the prevalence of hyper fibrinogenemia in Type 2DM. Patients with type 2 diabetes mellitus had a high prevalence of hyper fibrinogenemia. Levels slightly differed men and women. In men fibrinogen increased with age[11].

Hazra B, Sengupta N, Saha SK et al in their study on slusrna fibrinogen in stroke, reveled that the elevated plasma fibrinogen may be an important risk factor for the thrombotic ischaemic stroke[13].

Koenig et al provides an overview of recently accumulated evidence on the pathogenetic role of fibrinogen in various vascular beds, and tries to elucidate determinants for patients susceptibility so that subgroups at particular risk of severe clinical complications can be characterized more accurately[17].

Based on the considerable elevated risk of cardiovascular and cerebrovascular disease complications associated with increased levels of plasma fibrinogen, the potential value of lowering in the primary or secondary prevention of atherosclerotic disease is now recognized as an important topic for consideration[17].

Qizibash – N et al has been identified in two prospective observational studies. The importance of fibrinogen. The relationship has been followed to be independent of other haemostatic and haemorrheological factor (Eg. Von willebrand factor, Tissue plasminogen activator and packed cell volume). Fibrinogen should be considered a risk factor for lschaemic stroke and included in the assessment of Individual risk factors. Therefore, after blood pressure, fibrinogen is the most important potentilly treatable risk factor for ischaemic stroke. There are several mechanisms whereby fibrinogen could promote atherothromboembolism. Thrombosis through a hyper coagulable state, the acceleration of atherosclerosis, or the reduction of blood flow. Due to high blood or plasma viscosity. The mechanism, however, is unlikely to be mediated through high blood viscosity per se as secondary erythrocytosis (Another major

determinant of blood viscosity) has not consistently been found to be a risk factor for stroke. Fibrinogen should be considered a risk fator for ischaemic stroke and included in the assessment of individual risk factors[22].

Thavaraj V; Behari-M; Prasad K, et al carried out blood viscosity studies were in 14 patients with acute stroke, 8 with cerebral infarction, 6 with cerebral haemorrhage and in thirteen controls. We observed a statistically significant higher values of plasma, Red cell and whole viscosity in patients with acute stroke than in normal controls. Plasma fibrinogen levels were statistically higher ($P<0.01$) in patients than in normal controls. The platelet aggregation was increased in two young adults with acute stroke. The results suggest that the haemorrheological factors play an important role in the pathophysiology of stroke patients[26].

MATERIALS AND METHODS

Setting:

This study was carried out in the Department of medicine, Madurai Medical College and Government Rajaji Hospital, Madurai.

Period of Study:

1 year from Jun 2005 to May 2006.

Design of study:

This is a prospective study of consecutive patients with ischemic stroke admitted to Government Rajaji Hospital, Madurai.

Sample Size:

50 patients with ischemic stroke admitted in the Department of Medicine Government Rajaji Hospital, Madurai, and 50 controls of age and sex match were taken.

Inclusion Criteria:

All patients those who have presented with definitive signs of neurological deficit with CT proved ischemic stroke.

Exclusion criteria:

1. Individual with acute infection and inflammatory episode
2. Patients with valvular heart disease
3. Patients with clot in the left ventricular cavity

4. Patients with absent peripheral pulses
5. Pregnancy and Puerperium
6. Women on oral contraceptive pills
7. Moderate and severe Alcoholism.

METHODS:

HISTORY

Name, Age, Sex of each patient was noted. The presenting complaint of neurological deficit and the mode of onset was evaluated. Special emphasis was made to obtain the H/o head ache, H/o loss of consciousness, H/o Seizures, H/o Trauma to the head, H/o malignancy and H/o Oral contraceptive pills in females.

Past history of TIA, hypertension, diabetes mellitus, were carefully sought. Enquiry about alcoholism, smoking, pregnancy or recent delivery was done. Any similar illness in the family was noted.

GENERAL EXAMINATION

In general examination apart from the routine observations, special emphasis was made to identify the BMI, corneal arcus, status of peripheral vessels and carotid bruit.

CENTRAL NERVOUS SYSTEM EXAMINATION

Tests for higher cortical functions were performed in patients those who were conscious. Examination for cranial nerve dysfunction was done in detail in

patients who were conscious. Efforts were made to identify the cranial nerve dysfunction in all patients.

Examination of spinomotor system was done meticulously to identify the neurological deficit as complete or partial. Sensory system examination was done and hemianaesthesia if present was identified by clinical examination.

Cerebellar dysfunction if present was elicited in detail. Bladder and bowel involvement was noted down. Signs of meningial irritation, and increased intracranial tension, was elicited and noted down. Optic fundus was visualized in all cases to identify, diabetic retinopathy, hypertensive retinopathy, and papilloedema.

Other systems were also examined in detail.

INVESTIGATIONS:

Basic investigations such as Hb, Routine blood cell count, urine analysis for albumin, sugar deposit, blood sugar, urea serum creatinine and serum electrolytes total cholesterol were done.

Plasma fibrinogen, electrocardiography, echocardiography and CT scan of brain were done.

METHOD OF ASSAYING FIBRINOGEN IN PLASMA:

Normal plasma fibrinogen level ranges from 190 to 400mgs/ 100ml of plasma, however the level more than 250mgs% can be considered as a risk factor as far as cerebrovascular disease is concerned.

(Rapid Turbidometric method)

Principle: When sodium sulphite is added to plasma, it forms a turbidity as it has specific affinity towards plasma fibrinogen. This fibrinogen can be read in quantitative term by comparing it with artificial Protein standards:

Required Reagents

1. 0.2ml of heparinized (or) Oxalated plasma
2. 3.8 of 12.5% sodium sulphite

(12.5 gm of anhydrous Na_2 So_3/100ml in water) solution

Test Method

Wash 0.2ml of heparinized (or) Oxalated plasma into 3.8ml of freshly prepared 12.5% sodium sulphite solution. Shake, allow to stand for exactly 10min., shack again and read the turbidity by comparison with artificial protein standards.

A control with serum should be setup in case of deterioration of the sodium suphite; this should give no turbidity. The sodium suphite solution must be prepared from the dry salt immediately before use.

Fibrinogen = value of matching tube x 10 c.i.e. if the test matches the tube labeled equivalent to 10mg per 100 ml then the fibrinogen = 100mg / 100ml.

STATISTICAL ANALYSIS:

The figures collected were posted in a master chart. Statistical analysis was done using epidemiological package 2002 developed for WHO. Kruskall Wallis ‘Chi’ square test was used to find significance. A ‘P’ value less than 0.05 is taken to indicate significant difference among the variables.

OBSERVATION AND RESULTS

Table - 1

INCIDENCE IN RELATION TO AGE

AGE	NO. OF PATIENTS	PERCENTAGE	M/F
31-40	4	8%	3/1
41-50	11	22%	9/2
51-60	14	28%	11/3
61-70	17	34%	11/6
>71	4	8%	4/0

In the age group of 31 to 40 there Were 8% of which 3 are male and 1 female. There were 11 patients in age group of 41 to 50 comprising 22% of which 9 males and 2 females.

In the age group of 51 to 60 there were 11 males and 6 females comprising 28% of the total 7 patients were in the age group of 61 to 70 and 4 patients in the age group of greater than 71.

Table -2

INCIDENCE WITH RELATION TO SEX

Sex	NO. OF PATIENTS	PERCENTAGE
Male	38	76%
Female	12	24%

Among the 50 patients 76% of the patients were Male 24% were female

Table - 3

SIGNIFICANT HISTORY

HISTORY	NO. OF PATIENTS	PERCENTAGE
T1A	7	14%
Diabetes	30	60%
Hypertension	19	38%
Smoking	27	54%
IHD	11	22%

In our study 60% of the patients were associated with diabetes mellitus

54% patients were smokers.

38% of the patients associated with hypertension

22% of the patients had IHD and 14% of the patients had H/o TIA

Table -4

IMPORTANT SYMPTOMS

SYMPTOMS	NO. OF PATIENTS	PERCENTAGE
Head ache	20	40%
Loss of consciousness	15	30%
Seizures	6	12%
Trauma	-	6%
Vertigo	3	24%
Vomiting	12	-
Diplopia	3	6%
Dysphasia	29	58%
Facial deviation	47	94%
Dysphagia	4	8%

In our study 94% of the patients had Facial Deviation, 58% of the patients had Dysphasia, 40% of the patients had Head ache and 30% of the patients presented with loss of consciousness

24% of the patients complaint vomiting and 12% of the patients had Seizures. 8% of the patients had Dysphagia, 6% of the patients had Diplopia and 6% with vertigo

Table - 5

IMPORTANT SIGNS

SIGNS	NO. OF PATIENTS	PERCENTAGE
Carotid bruit	2	4%
Cranial nerve dysfunction Other than UMN type of VII nerve	6	12%
Hemianaesthesia	3	6%
Hemianopia	1	2%
Bladder dys function	10	20%
Signs of increased ICT	6	12%
Papilloedema	6	12%

In our study 20% of the patients had Bladder dysfunction.

12% of the patients had Signs of increased ICT.

12% of the patients had Papilloedema.

12% of the patients had cranial nerve dysfunction other than UMN type of seventh nerve palsy.

6% of the patients had Hemianaesthesia.

2% of the patients had Hemianopia

Table - 6

AGE AND PLASMA FIBRINOGEN

Age Group	Cases		Controls	
	Mean	SD	Mean	SD
31-40	345	128.7	187.5	34.8
41-50	334.5	79.5	219.1	60.8
51-60	382.2	149.4	277.9	701.7
61-70	414.7	134.6	276.8	83
>70	440	84.8	311.3	43.3
p Value	0.4071		0.0128	

Our study shows there was significant difference in plasma fibrinogen level between different age group in both cases and control the relationship between age and plasma fibrinogen level was statistically not significant in cases(P= 0.4071)and significant in controls (P= 0.0128)

Table -7

SEX AND PLASMA FIBRINOGEN

Sex	Cases		Controls	
	Mean	SD	Mean	SD
Male	384.5	125	275	75.2
Female	384.2	134.1	200	53.9
p Value	0.9185		0.0066	

In our study there was no statistically difference between sex and plasma fibrinogen level of cases (P= 0.9185) while controls showed statistically significant difference (P= 0.0066)

Table - 8

DM AND PLASMA FIBRINOGEN

DM	Cases		Controls	
	Mean	SD	Mean	SD
Diabetes	435.5	128.3	320.5	60.1
Non Diabetes	307.8	73.7	212.5	47.6
p Value	0.0004		0.0001	

In our study there was a statistically significant difference between diabetics and non diabetics in both cases (P= 0.0004) and in controls (P= 0.0001)

Table - 9

PLASMA FIBRINOGEN IN DM OF CASES VS CONTROL

DM	PLASMA FIBRINOGEN	
	Mean	SD
CASES CONTROLS	435.5 32.5	128.3 60.1
p Value	P 0.0006	

This table shows there was a statistically significant difference in plasma fibrinogen in diabetics of cases and controls (P= 0.0006)

Table - 10

HT AND PLASMA FIBRINOGEN

HT	Cases		Controls	
	Mean	SD	Mean	SD
HT	431.3	123.5	300.6	81.6
Non HT	355.7	120.3	239.1	64.1
p Value	0.0324		0.0184	

There was a statistically significant difference in plasma level in hypertensives and non hypertensives of both cases (P= 0.0324) and controls (P= 0.0184)

Table - 11

PLASMA FIBRINOGEN IN HT CASES Vs CONTROLS

Hypertension	Plasma fibrinogen	
	Mean	SD
Cases	431.3	123.5
Controls	300.6	81.6
p Value	0.0012	

In this study plasma fibrinogen was statistically significant difference in hypertensive cases and hypertensive controls (P= 0.0012)

Table - 12

SMOKING AND PLASMA FIBRINOGEN

Smoking	Cases		Controls	
	Mean	SD	Mean	SD
Smokers	338.9	118.4	283.9	83.4
Non Smokers	313.2	112.8	265.9	64.8
p Value	0.438		0.6807	

There was no statistically significant difference in plasma fibrinogen levels in smoker and nonsmokers of both cases (P= 0.438) in controls (P= 0.6807)

Table 13

PLASMA FIBRINOGEN IN SMOKERS CASES Vs CONTROLS

GROUP	PLASMA FIBRINOGEN	
	Mean	SD
Cases	338	118.4
Controls	283	83.4
p Value	0.0064	

Plasma fibrinogen level was statistically significant difference in smokers of cases and controls (P= 0.0064)

Table - 14

CHOLESTEROL AND PLASMA FIBRINOGEN

Cholesterol	Cases		Controls	
	Mean	SD	Mean	SD
<200mg/dl	349.5	120.3	242.1	63
>200mg/dl	441.3	116.1	370	50.7
p Value	0.0053		0.0002	

In our study there was a statistically significant difference in plasma fibrinogen level in patients with hypercholesterolemia and normal cholesterol level of both cases (P=0.0053) and controls (P= 0.0002)

Table 15

PLASMA FIBRINOGEN IN HYPERCHOLESTROLEMIA

CASES Vs CONTROLS

GROUP	Plasma Fibrinogen	
	Mean	SD
Cases	441.3	116.1
Controls	370	50.7
p Value	0.1834	

In our study there was no statistically significant difference in hypercholesterolemia of cases and controls (P=0.1834)

Table - 16

BMI AND PLASMA FIBRINOGEN

BMI	Cases		Controls	
	Mean	SD	Mean	SD
<23	246.2	76.5	236.2	59.2
>23	386.9	113.9	310.7	83.5
P value	0.0001		0.0024	

There was a statistically significant difference in obesity and plasma fibrinogen level in both cases (P= 0.0001) in controls (P=0.0024)

Table - 17

PLASMA FIBRINOGEN AND OBESITY

CASES Vs CONTROLS

GROUP	Plasma Fibrinogen	
	Means	SD
Cases	419.1	110.2
Controls	310.7	83.5
P value	0.0027	

There was a statistically significant difference in cases and controls with increased BMI (P=0.0027)

Table 18

PLASMA FIBRINOGEN IN CASES Vs CONTROL

Group	Plasma Fibrinogen	
	Mean	SD
Cases	384.4	125.8
Controls	260	75.5
p Value	0.0001	

In our study there was a statistically significant difference in plasma fibrinogen level of cases and controls (P= 0.0001)

DISCUSSION

In the study population of 50 patients, the age of patients ranged from 33 years to 81 years. There were 4 patients in age group of 31 to 40 includes 3 male and 1 female. There were 11 patients in 41 to 50 age group includes 9 males and 2 females. In the age group of 51 – 60 there were 14 patients of which 11 were male 3 were female. 17patients in the age group of 61-70 of which 11 were males and 6 were females and 4 male patients in the age group of more than 71.

In those 50 patients 38 were male 12 were female patients indicating a male predominance

The incidence of major vascular risk factors was analysed, diabetes mellitus was found in 60% of the patients hypertension was found in 38% of the patients. Smoking was present in 54% of the patients. History of coronary artery disease was present in 22% of the patients previous history of TIA was present in 14% of patients hypercholesterolemia found in 38% of the patients. BMI more than 23 found in 38 patients.

Analysis of the signs and symptoms of the patients shows facial deviation present in 94% of patients. head ache in 20% of the patients. Loss of consciousness present in 22% of the patients. 12% of the patients had seizures. Vomiting present in 24% of the patients.

Plasma fibrinogen level was significantly increased with age advance in the control group not in the cases. Male has high plasma fibrinogen value than female in the control group

Plasma fibrinogen level was increased in hypertension, diabetes, obesity and hyperchloesterolemia. This is correlate with Pai Mahesh C. et al and Lee et al study. But there is no significant difference in smokers and non smokers.

When plasma fibrinogen levels in stroke group with one risk factor compared with control group with same risk factor a statistically difference found in diabetes, hypertension smokers and obese patients. This is correlate with Pai Mahesh C. et al study. But there is no significant difference in patients with hypercholesterolemia.

A statistically significant raise in plasma fibrinogen level was observed in the stroke patients compared to that in the control group. This is correlates with Pai Mahesh C. et al and Harza B et al study

CONCLUSION

- This study shows the association of elevated level of plasma fibrinogen in stroke patients compared to the age and sex matched control population.
- Plasma fibrinogen level was significantly elevated in other major risk factor for stroke like hypertension, diabetes, obesity and hypercloesterolemia.

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ABBREVIATION

ACA	-	Anterior Cerebral Artery
BMI	-	Body Mass index
CT	-	Computerised Tomography
CVA	-	Cerebrovascular Accident
CVD	-	Cerebrovascular Disease
DM	-	Diabetes Mellitus
FPA	-	Fibrinopeptide - A
FPB	-	Fibrinopeptide -B
HT	-	Hypertension
IHD	-	Ischaemic heart disease
MCA	-	Middle cerebral artery
MRI	-	Magnetic Resonance Imaging
P	-	‘P’ Value
PACS	-	Partial Anterior Circulation Syndrome
PCA	-	Posterior cerebral artery
SD	-	Standard Deviation
TACS	-	Total Anterior Circulation Syndrome
TIA	-	Transient Ischaemic attack
WHO	-	World health organization

PROFORMA

NAME: AGE: SEX:

I.P.NO: OCCUPATION

ADDRESS

PRESENT ILLNESS:

Time and Mode of onset

H/O Head Ache	H/O LOC	H/O Seizures
H/O Trauma	H/O Vertigo	H/O Diplopia
H/O Vomiting	H/O Dysphasia	H/O Dysphagia

PAST ILLNESS

H/O TIA	H/O Diabetes	H/O Hypertension
H/O Tuberculosis	H/O Smoking	H/O Angina / IHD

GENERAL EXAMINATION

Anaemia	Obesity	Corneal Arcus
Carotid Bruit	Pulse	BP
Peripheral Vessels	Fundus.	

CNS

Higher Function

Cranial Nerves

SPINOMOTOR SYSTEM

Hemiplegia / Hemiparesis

SENSORY SYSTEM

Hemianaesthisa

CEREBELLUM

SPINE AND CRANIUM

OTHER SYSTEMS EXAMINATION

INVESTIGATIONS:

Urine	Albumin	Sugar	Deposit
Blood	Sugar	Urea	
Serum	Cholesterol	ESR	

Plasma Fibrinogen

ECG 12 Leads

Echo cardiography

CT Scan Brain.

MASTER CHART CASES

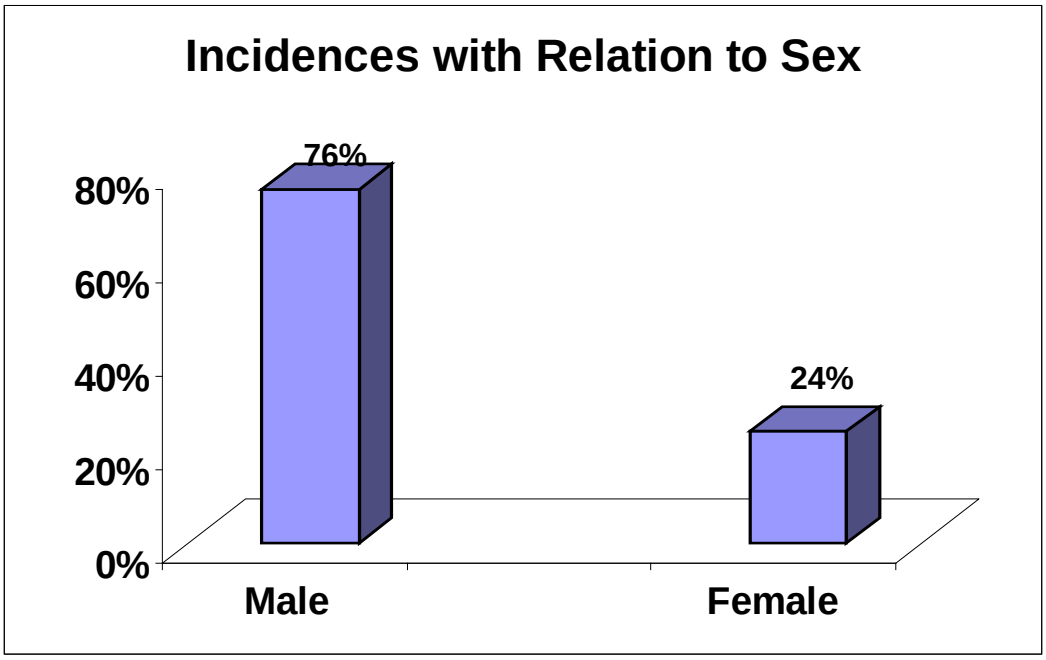
S.No.	Name	GROUP	Age	Sex	Smoking	DM	HT	Cholesterol	BMI	Plasma Fibrinogen
1	Venugobal	Cases	48	Male	Yes	No	No	156	26.71	290
2	Ponnaiyan	Cases	46	Male	Yes	Yes	No	270	25.36	370
3	Chithambram	Cases	39	Male	No	Yes	No	255	28.2	380
4	Murugan	Cases	33	Male	Yes	Yes	No	225	24.2	510
5	Saraswathi	Cases	42	Female	No	Yes	Yes	242	24.01	490
6	Vasnatha	Cases	35	Female	No	No	Yes	175	25.71	270
7	Muthu	Cases	38	Male	Yes	No	No	180	21	245
8	Sundaram	Cases	45	Male	Yes	No	No	161	22.4	245
9	Shanthakumar	Cases	42	Male	No	Yes	No	210	21.4	275
10	Velathal	Cases	47	Female	No	Yes	Yes	230	23.04	410
11	Andiappan	Cases	55	Male	Yes	No	No	110	22.7	260
12	Duraipandi	Cases	61	Male	Yes	No	No	210	26.71	320
13	Rajalakshmi	Cases	61	Female	No	Yes	No	189	21.9	245
14	Alaharsamy	Cases	58	Male	Yes	No	No	146	23.04	280
15	Chellammal	Cases	63	Female	No	Yes	Yes	210	28.8	270
16	Pitchai	Cases	61	Male	Yes	No	No	156	24.01	295
17	Duraisamy	Cases	62	Male	No	Yes	Yes	273	24.01	495
18	Kuppusamy	Cases	75	Male	No	No	No	180	23.2	345
19	Pandi	Cases	56	Male	Yes	Yes	No	145	23.01	430
20	Manogaran	Cases	46	Male	Yes	No	No	175	24.01	355
21	Mahalingam	Cases	48	Male	No	No	Yes	100	25.75	350
22	Muthammal	Cases	61	Female	No	Yes	No	166	24.01	445
23	Pandian	Cases	66	Male	Yes	Yes	Yes	156	26.71	295
24	Panchu	Cases	81	Male	No	Yes	Yes	225	28.2	550
25	Subbyah	Cases	73	Male	Yes	No	Yes	166	24.01	445
26	Raman	Cases	72	Male	Yes	Yes	No	136	24.01	420

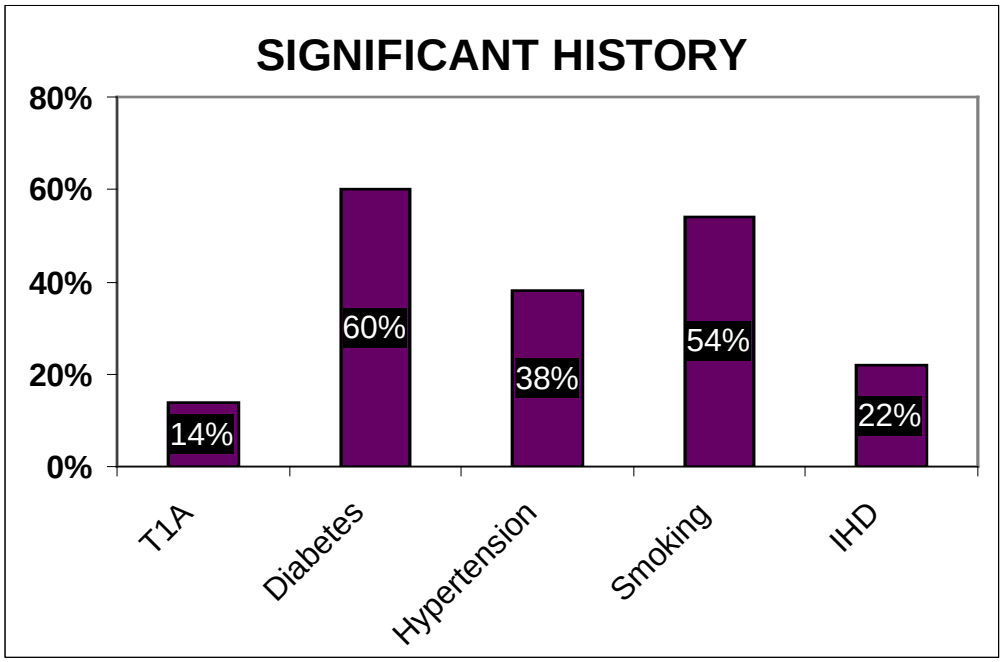
S.No.	Name	GROUP	Age	Sex	Smoking	DM	HT	Cholesterol	BMI	Plasma Fibrinogen
27	Seemaisamy	Cases	62	Male	No	Yes	Yes	216	24.01	295
28	Kasi	Cases	55	Male	No	No	No	105	22	236
29	Palaniappan	Cases	51	Male	Yes	No	No	225	26.71	360
30	Valliammal	Cases	60	Female	No	Yes	No	180	22.4	620
31	Panchavarnam	Cases	56	Female	No	Yes	No	180	24.01	345
32	Kumarayi	Cases	65	Female	No	Yes	Yes	246	27.48	320
33	Muthuvel	Cases	55	Male	Yes	Yes	Yes	266	24.01	505
34	Gunasekaran	Cases	56	Male	Yes	Yes	Yes	175	24.01	645
35	Ismail	Cases	62	Male	No	Yes	No	275	24.01	630
36	Maruthai	Cases	53	Female	No	Yes	Yes	140	24.01	420
37	Veeranan	Cases	62	Male	Yes	No	No	108	20.8	255
38	Periaveeran	Cases	56	Male	Yes	Yes	Yes	210	30.48	620
39	Rahimabdulla	Cases	51	Male	Yes	Yes	Yes	260	26.71	550
40	Kandasamy	Cases	49	Male	Yes	No	No	190	24.71	395
41	Kumarasamy	Cases	48	Male	Yes	No	No	155	21.3	250
42	Krisha aayar	Cases	64	Male	Yes	Yes	No	256	24.01	490
43	Thangavel	Cases	56	Male	No	Yes	Yes	140	28.2	260
44	Seenithevar	Cases	63	Male	Yes	Yes	Yes	165	28.04	460
45	Muthurajan	Cases	65	Male	No	No	No	166	23.03	490
46	Swaminathan	Cases	52	Male	Yes	No	No	165	20.5	245
47	Balakrishnan	Cases	65	Male	Yes	Yes	Yes	256	27.29	545
48	Rakkayi	Cases	65	Female	No	Yes	No	146	32.29	580
49	Perumal samy	Cases	45	Male	Yes	No	No	175	20.9	250
50	Ramayammal	Cases	53	Female	No	Yes	No	180	20.4	195

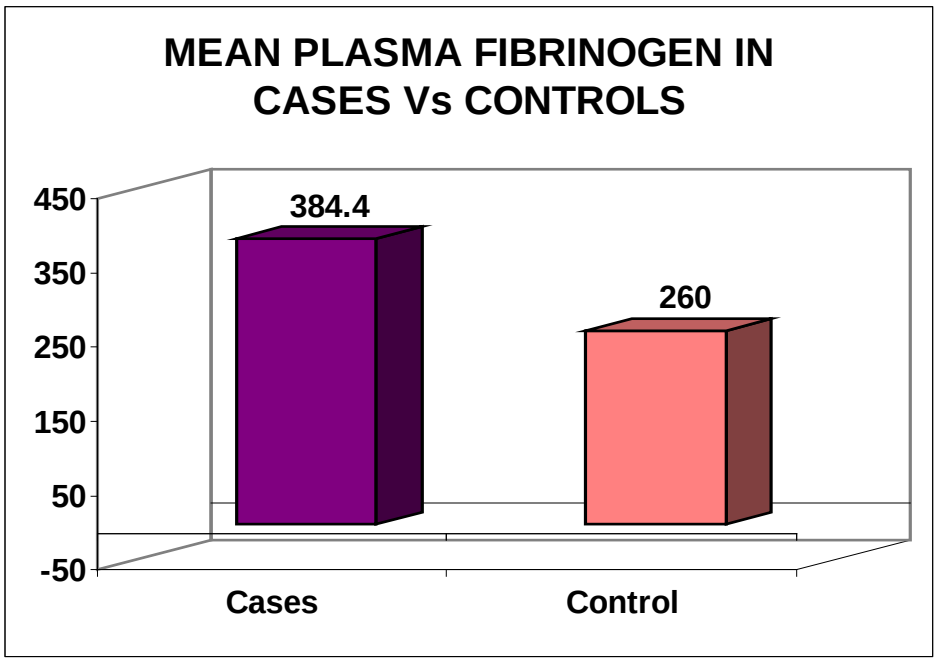
CONTROLS

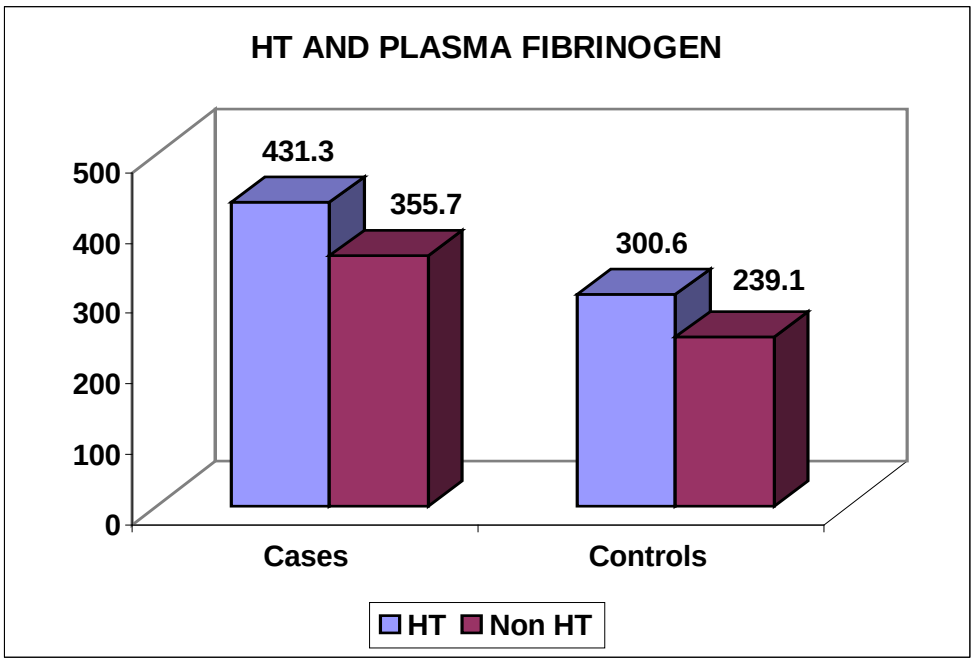
S.No.	Name	GROUP	Age	Sex	Smoking	DM	HT	Cholesterol	BMI	Plasma Fibrinogen
51	Kandasamy	Control	49	Male	Yes	Yes	No	226	20.37	355
52	Pandi	Control	45	Male	No	No	Yes	136	23.2	155
53	Devi	Control	63	Female	Yes	No	No	162	21.09	170
54	Singaram	Control	62	Male	Yes	No	No	116	20.37	270
55	Kesavan	Control	55	Male	Yes	No	No	96	20.27	205
56	Susai	Control	56	Male	Yes	No	No	136	19.5	255
57	Veeran	Control	51	Male	Yes	No	Yes	166	22.4	265
58	Arasi	Control	65	Female	No	Yes	Yes	186	22.4	235
59	Devathasan	Control	75	Male	No	Yes	No	160	31.88	315
60	Kamaraj	Control	71	Male	Yes	Yes	No	156	26.71	370
61	Asaithambi	Control	51	Male	Yes	No	Yes	186	24.01	336
62	Kalayani	Control	38	Male	Yes	No	No	120	22.4	155
63	Rajendran	Control	33	Male	Yes	No	No	125	20.27	220
64	Chinnasamy	Control	47	Male	No	Yes	Yes	185	20.27	290
65	Raja	Control	65	Male	Yes	Yes	Yes	246	30.48	410
66	Ramaiya	Control	56	Male	Yes	Yes	No	185	21.64	370
67	Paramasivam	Control	62	Male	Yes	No	No	166	20.27	255
68	Velusamy	Control	63	Male	No	Yes	Yes	196	24.01	365
69	Chellammal	Control	66	Female	No	No	No	166	18.9	155
70	Ponnambalam	Control	80	Male	No	Yes	No	146	24.01	290
71	Narayanan	Control	55	Male	No	Yes	No	146	20.4	275
72	Mohaiddin	Control	46	Male	No	No	No	106	20.27	155
73	Arumugam	Control	46	Male	No	No	Yes	200	22.4	215
74	Gurusamy	Control	61	Male	Yes	No	No	96	18.9	240
75	Karuppusamy	Control	62	Male	No	No	Yes	116	30.48	240
76	Rangasamy	Control	65	Male	No	Yes	No	144	31.88	305

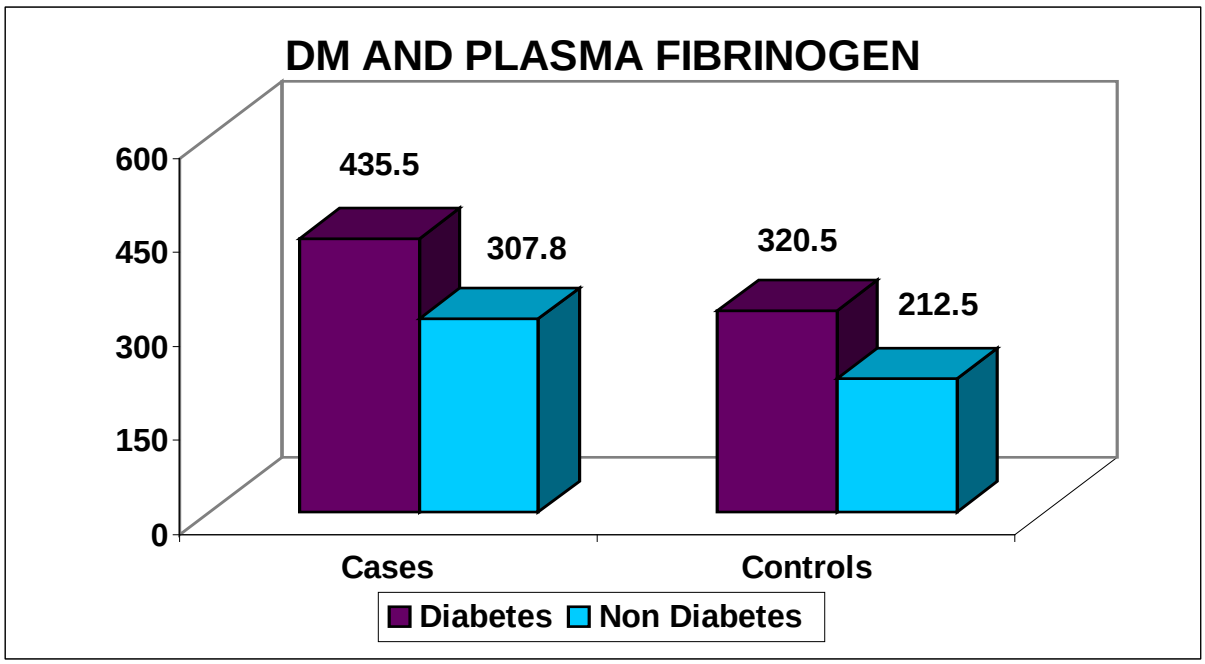
S.No.	Name	GROUP	Age	Sex	Smoking	DM	HT	Cholesterol	BMI	Plasma Fibrinogen
77	Nachiyappan	Control	63	Male	Yes	Yes	Yes	240	28.2	405
78	Periyasamy	Control	55	Male	No	Yes	Yes	210	22.4	365
79	Ochammal	Control	42	Female	No	Yes	Yes	180	22.4	230
80	Rasathi	Control	60	Female	No	No	Yes	216	22.4	265
81	Jeevaraj	Control	56	Male	Yes	Yes	Yes	260	26.71	390
82	Pandiyammal	Control	56	Female	Yes	No	No	165	19.46	150
83	Muniyandi	Control	48	Male	Yes	No	No	110	19.5	165
84	Eswari	Control	47	Female	No	Yes	No	156	18.9	240
85	Ganeshan	Control	42	Male	Yes	No	No	110	18.9	220
86	Vasuki	Control	35	Female	No	No	No	116	22.4	160
87	Prabakaran	Control	56	Male	No	Yes	No	125	22.4	260
88	Rasathi	Control	53	Female	No	No	Yes	186	17.55	200
89	Muniyammal	Control	61	Female	No	No	No	105	21.09	230
90	Sundrammal	Control	65	Female	No	No	No	136	24.01	160
91	Sivasami	Control	62	Male	Yes	No	No	156	20.27	255
92	Arumugam	Control	72	Male	No	Yes	No	166	29.41	270
93	Muniyasamy	Control	61	Male	No	Yes	Yes	184	24.01	345
94	Natchimuthu	Control	61	Male	Yes	Yes	Yes	236	28.2	400
95	Kannan	Control	58	Male	No	No	No	106	20.27	255
96	Kaliyammal	Control	53	Female	No	Yes	No	184	21.64	325
97	Karunakaran	Control	52	Male	No	Yes	No	166	22.4	240
98	Muthaiyah	Control	48	Male	No	No	No	110	18.9	180
99	Kumarasamy	Control	45	Male	Yes	No	No	145	21.09	205
100	Sadaiyandi	Control	39	Male	Yes	No	No	86	23.2	215

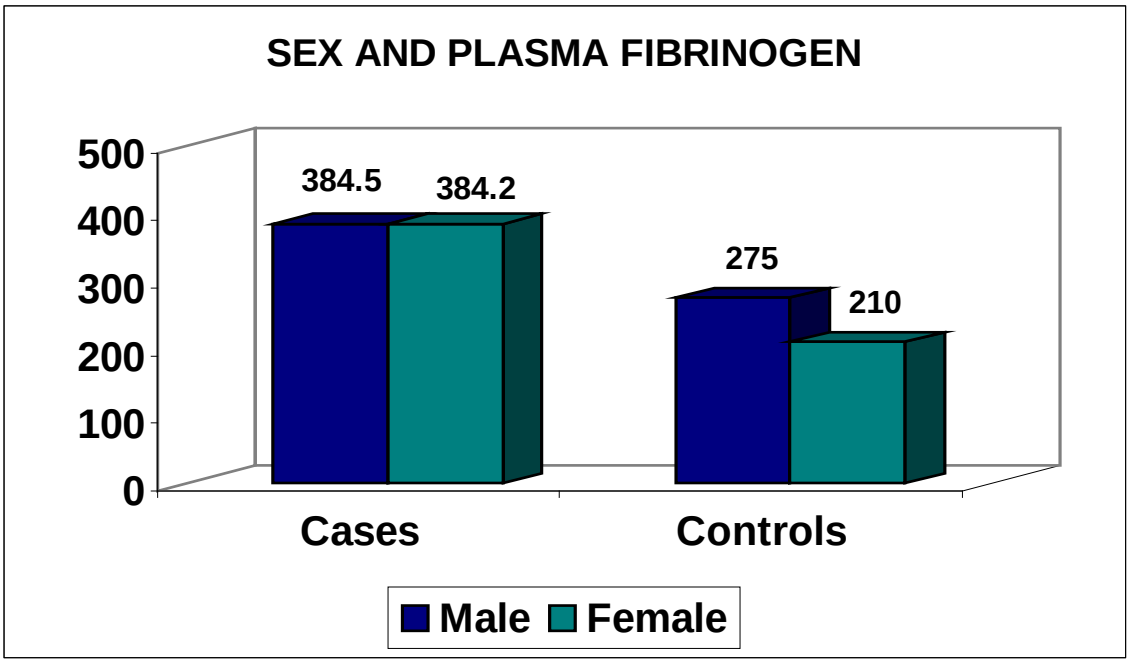

Incidences with Relation to Sex
76%
24%
80%
60%
40%
20%
0%
Male
Female

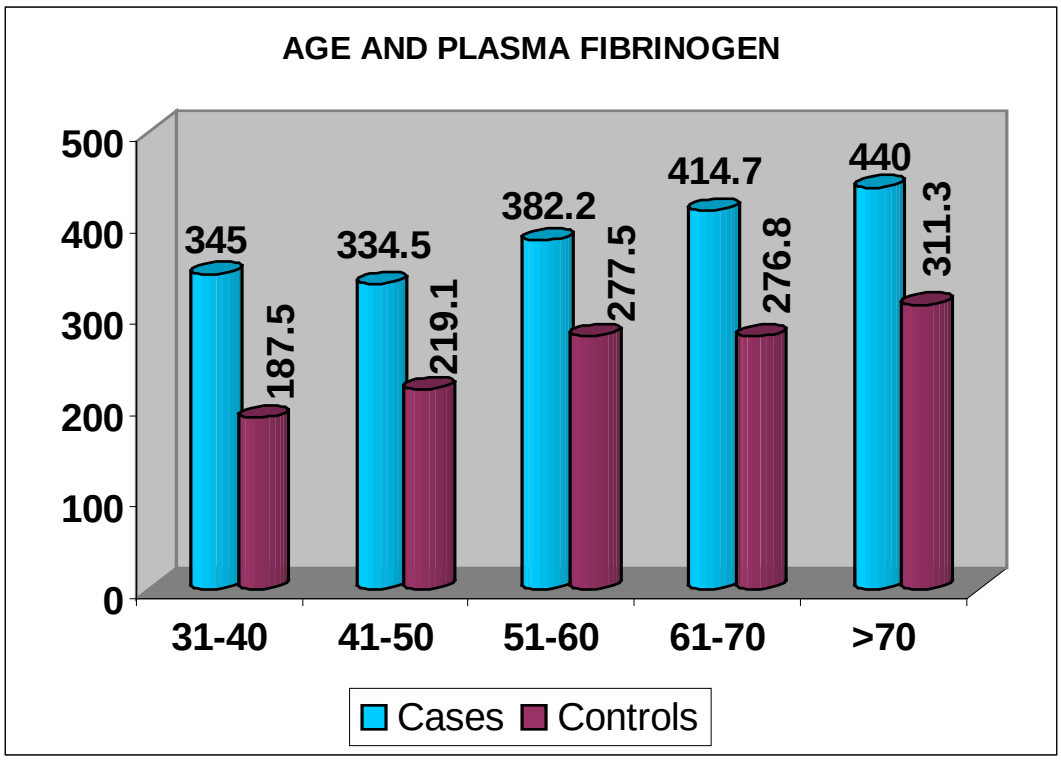

SIGNIFICANT HISTORY
80%
60%
40%
20%
0%
14%
60%
38%
54%
22%
T1A
Diabetes
Hypertension
Smoking
IHD

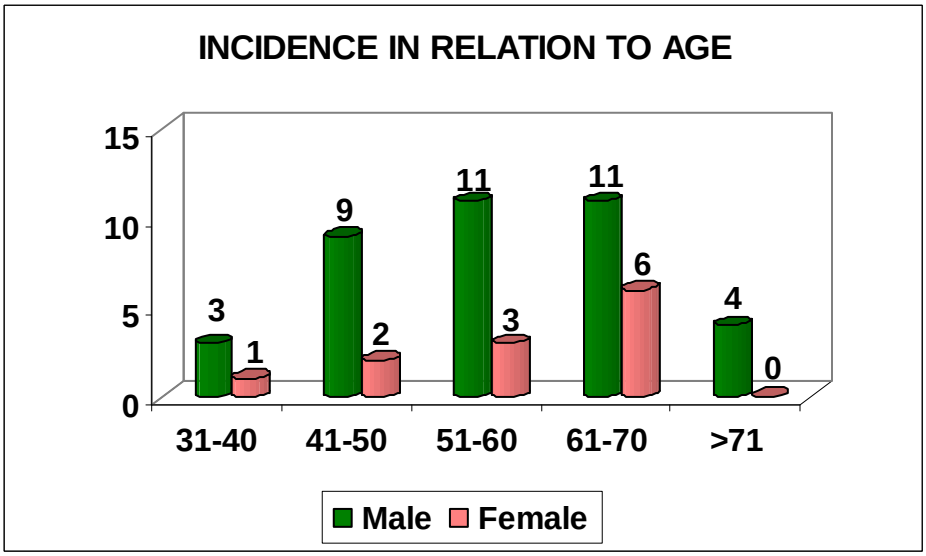

MEAN PLASMA FIBRINOGEN IN CASES Vs CONTROLS
450
350
250
150
50
-50
384.4
260
Cases
Control

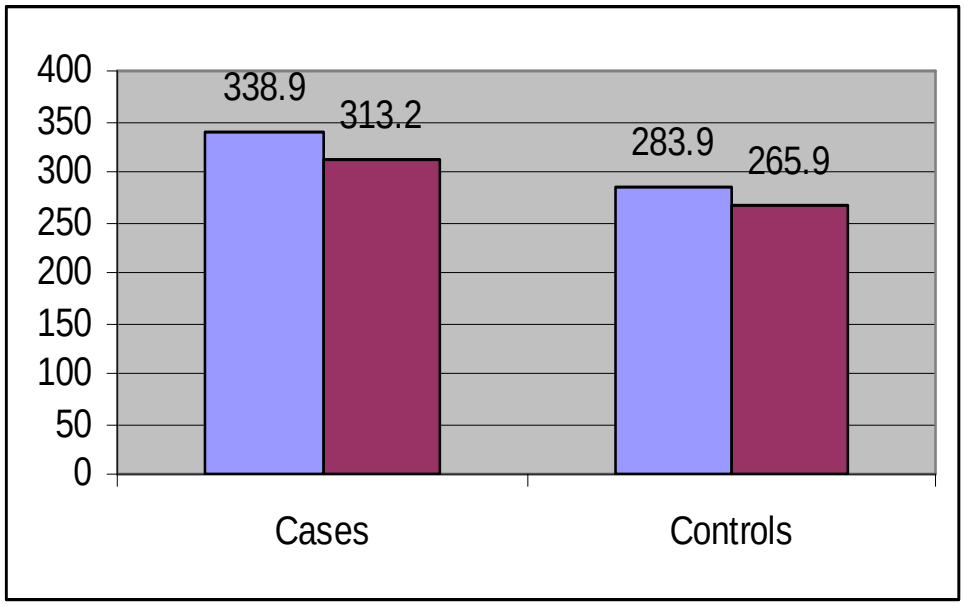

HT AND PLASMA FIBRINOGEN
500
400
300
200
100
0
431.3
355.7
300.6
239.1
Cases
Controls
HT
Non HT

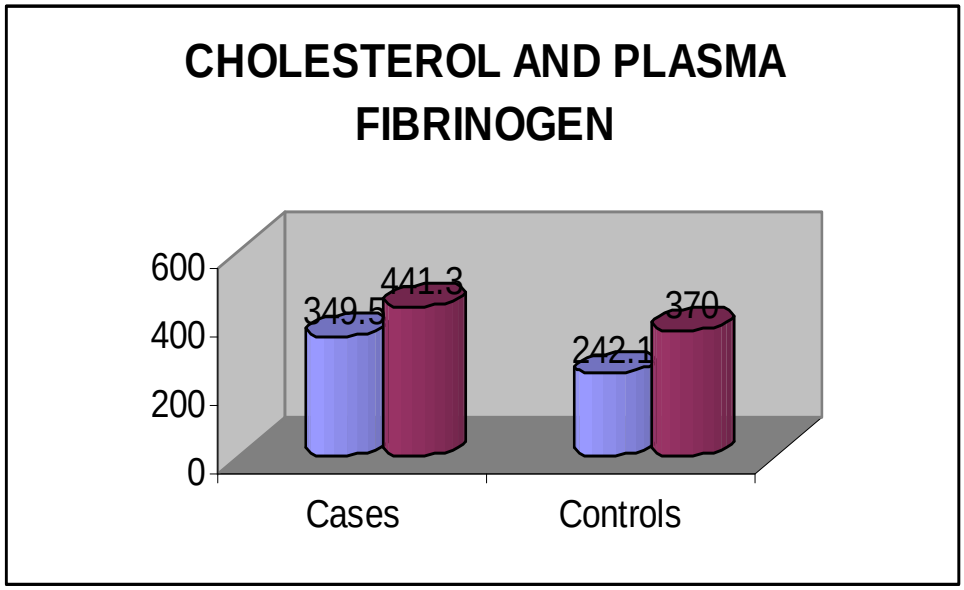

DM AND PLASMA FIBRINOGEN
600
450
300
150
0
435.5
307.8
320.5
212.5
Cases
Controls
Diabetes
Non Diabetes

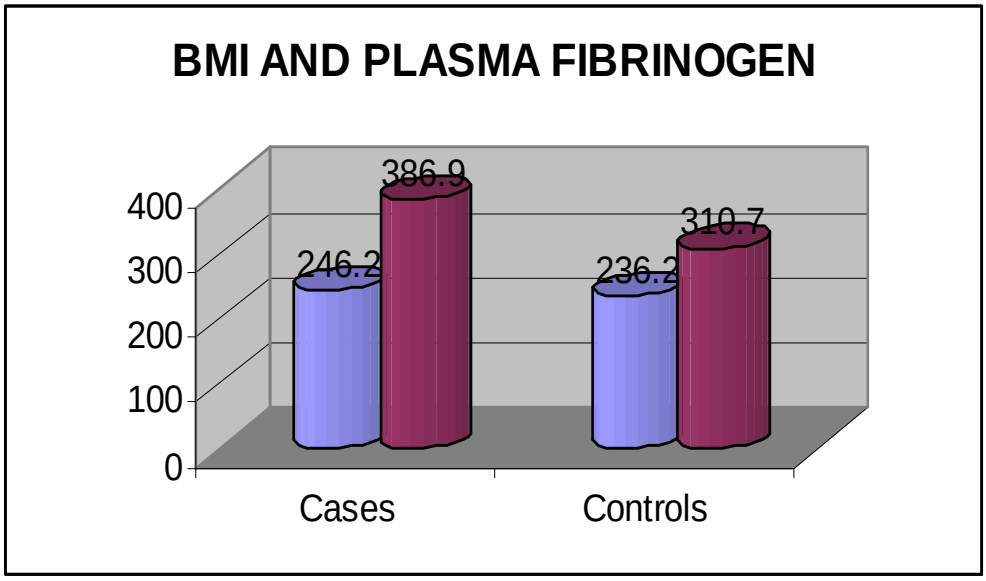

SEX AND PLASMA FIBRINOGEN
500
400
300
200
100
0
384.5
384.2
275
210
Cases
Controls
Male
Female

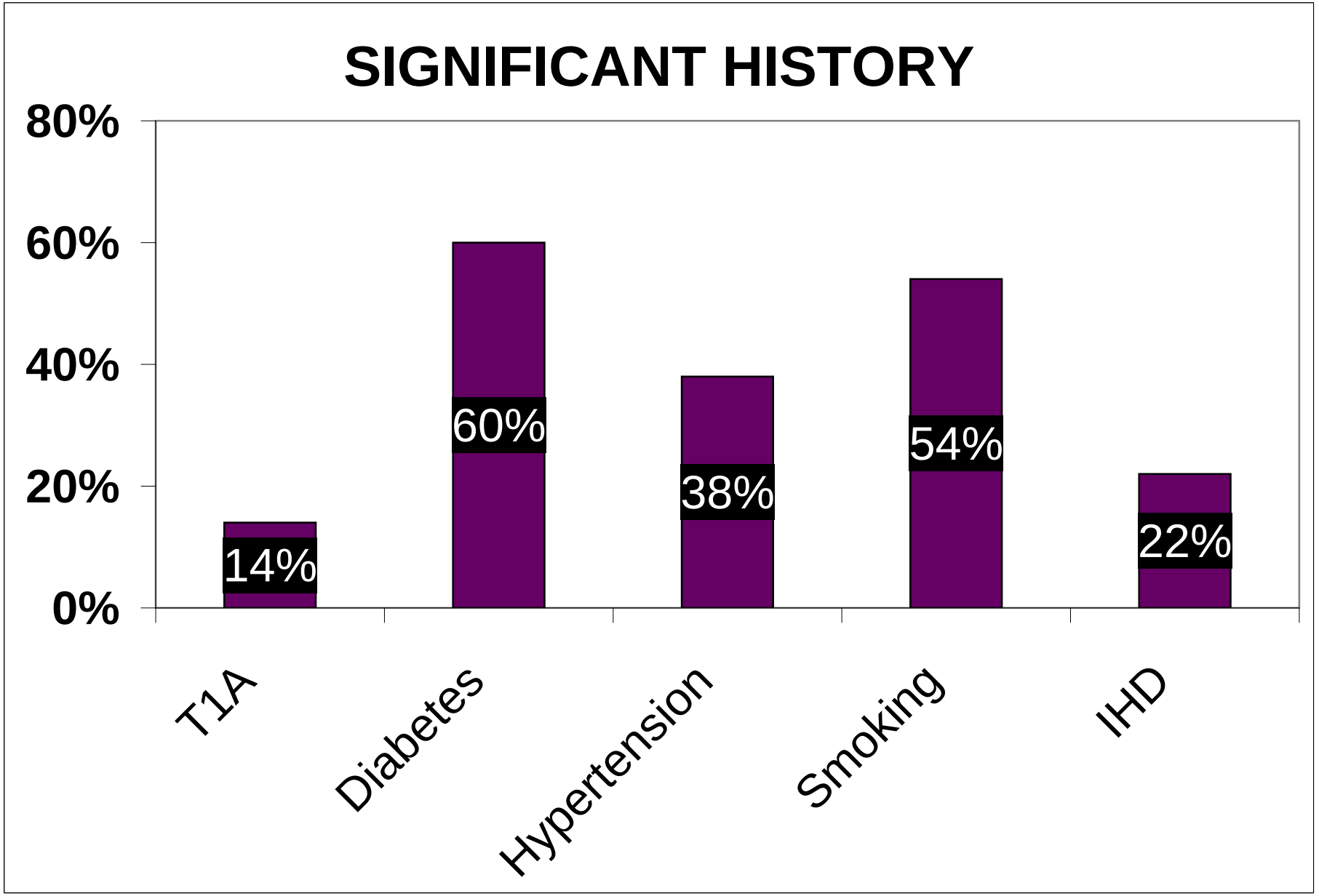

AGE AND PLASMA FIBRINOGEN
500
400
300
200
100
0
345
187.5
334.5
219.1
382.2
277.5
414.7
276.8
440
311.3
31-40
41-50
51-60
61-70
>70
Cases
Controls


INCIDENCE IN RELATION TO AGE
15
10
5
0
3
1
9
2
11
3
11
6
4
0
31-40
41-50
51-60
61-70
>71
Male
Female

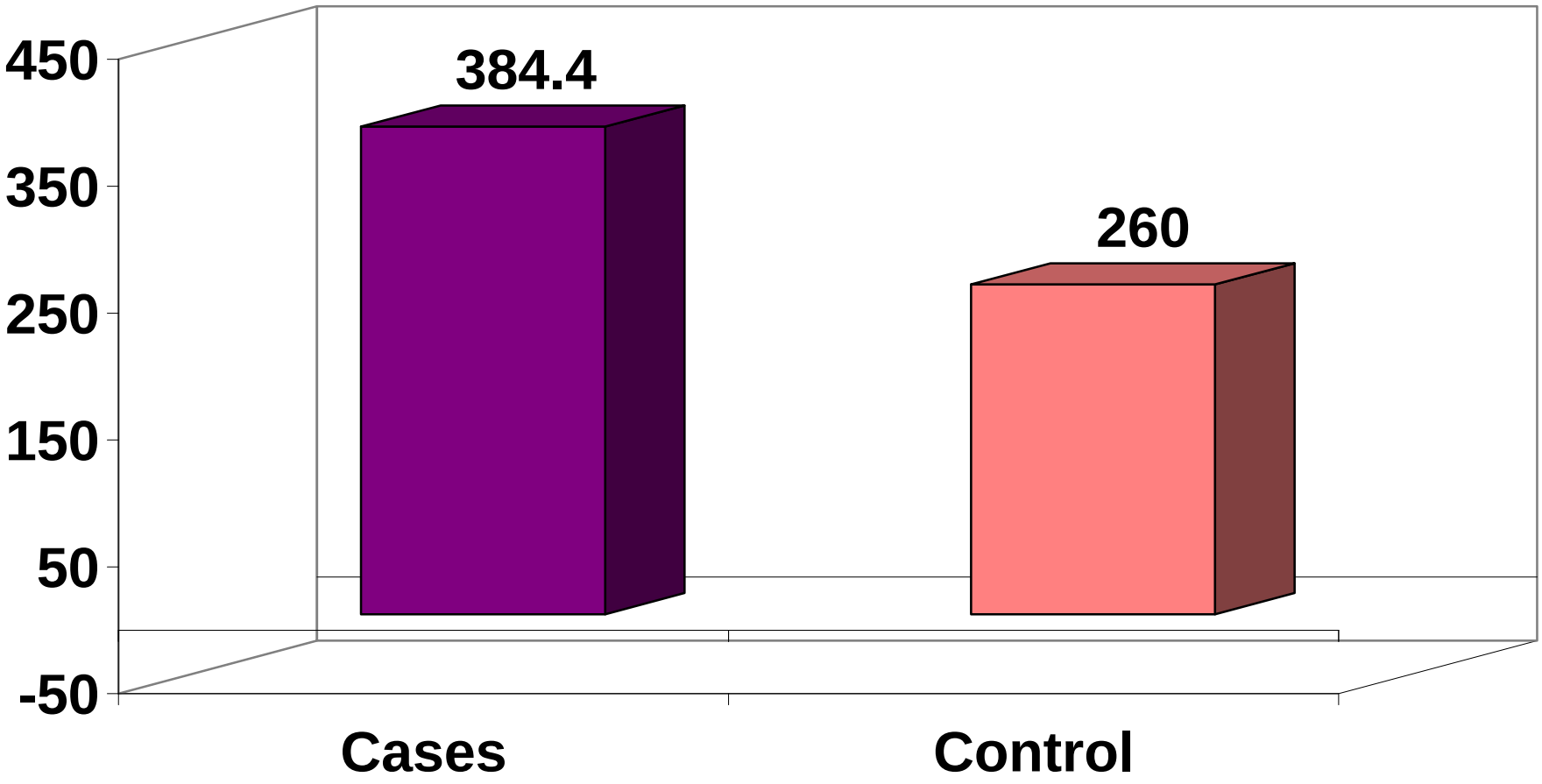

400
350
300
250
200
150
100
50
0
338.9
313.2
283.9
265.9
Cases
Controls

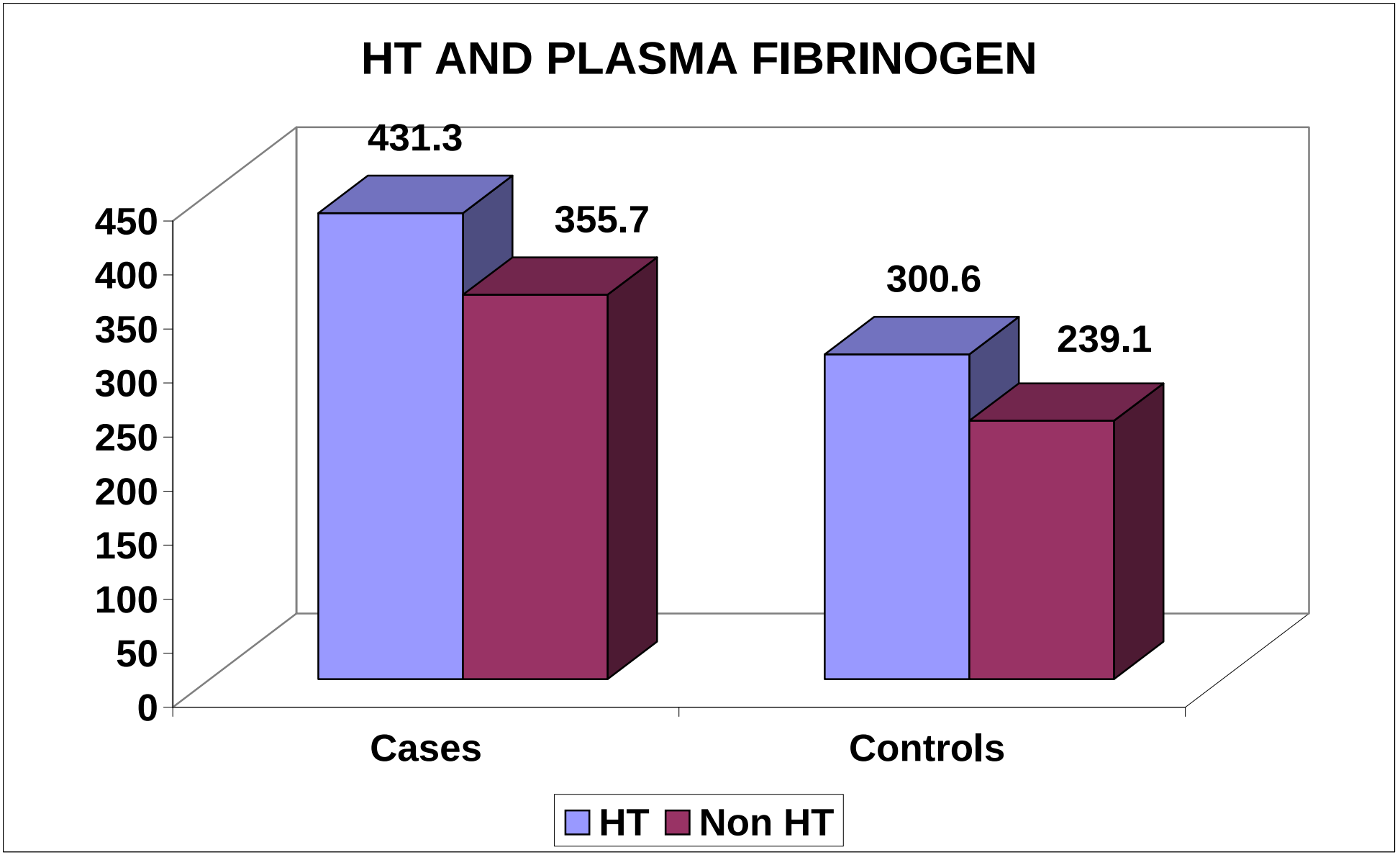

CHOLESTEROL AND PLASMA FIBRINOGEN
600
400
200
0
349.5
441.3
242.1
370
Cases
Controls

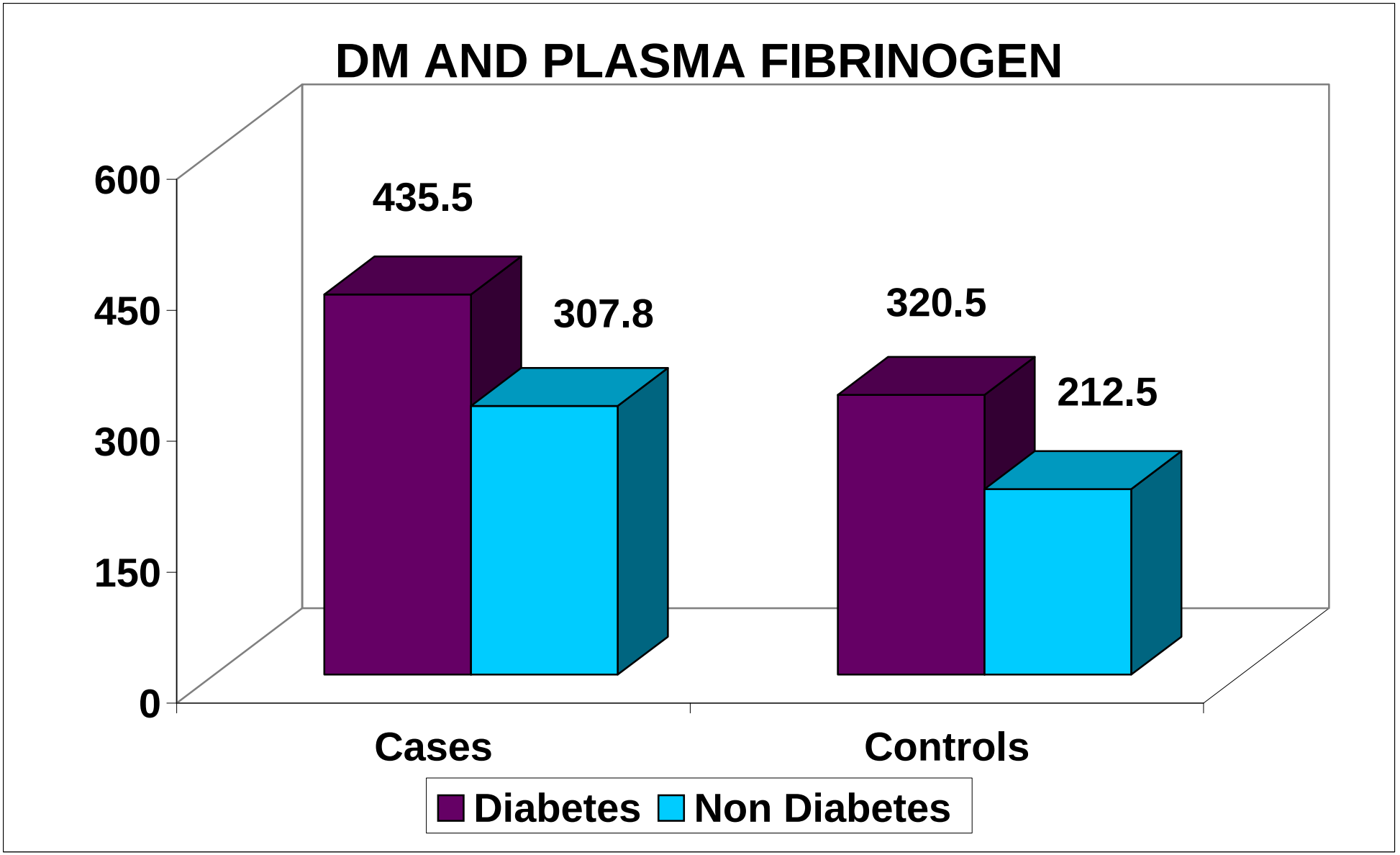

BMI AND PLASMA FIBRINOGEN
400
300
200
100
0
386.9
246.2
310.7
236.2
Cases
Controls

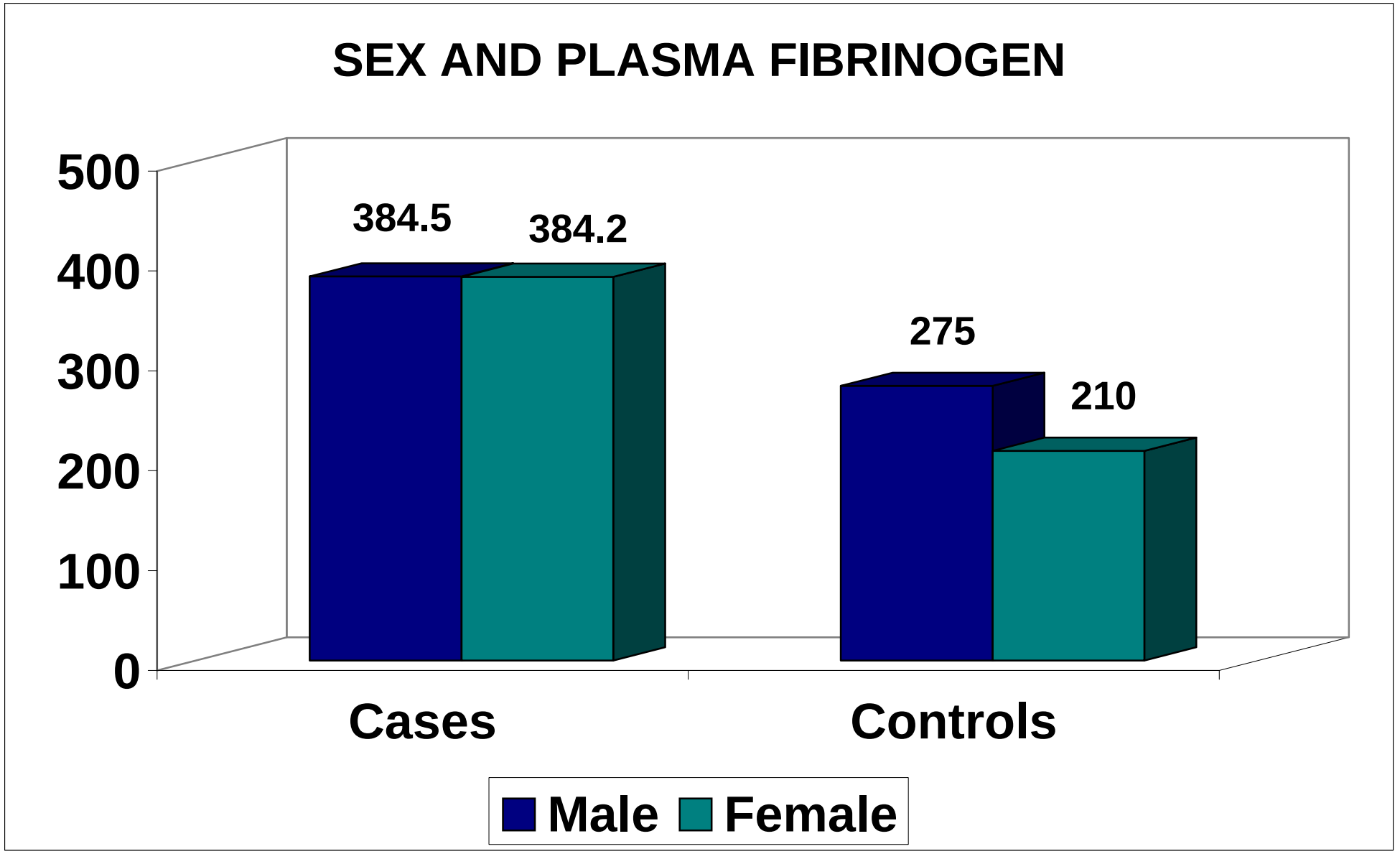

SIGNIFICANT HISTORY
80%
60%
40%
20%
0%
14%
60%
38%
54%
22%
T1A
Diabetes
Hypertension
Smoking
IHD

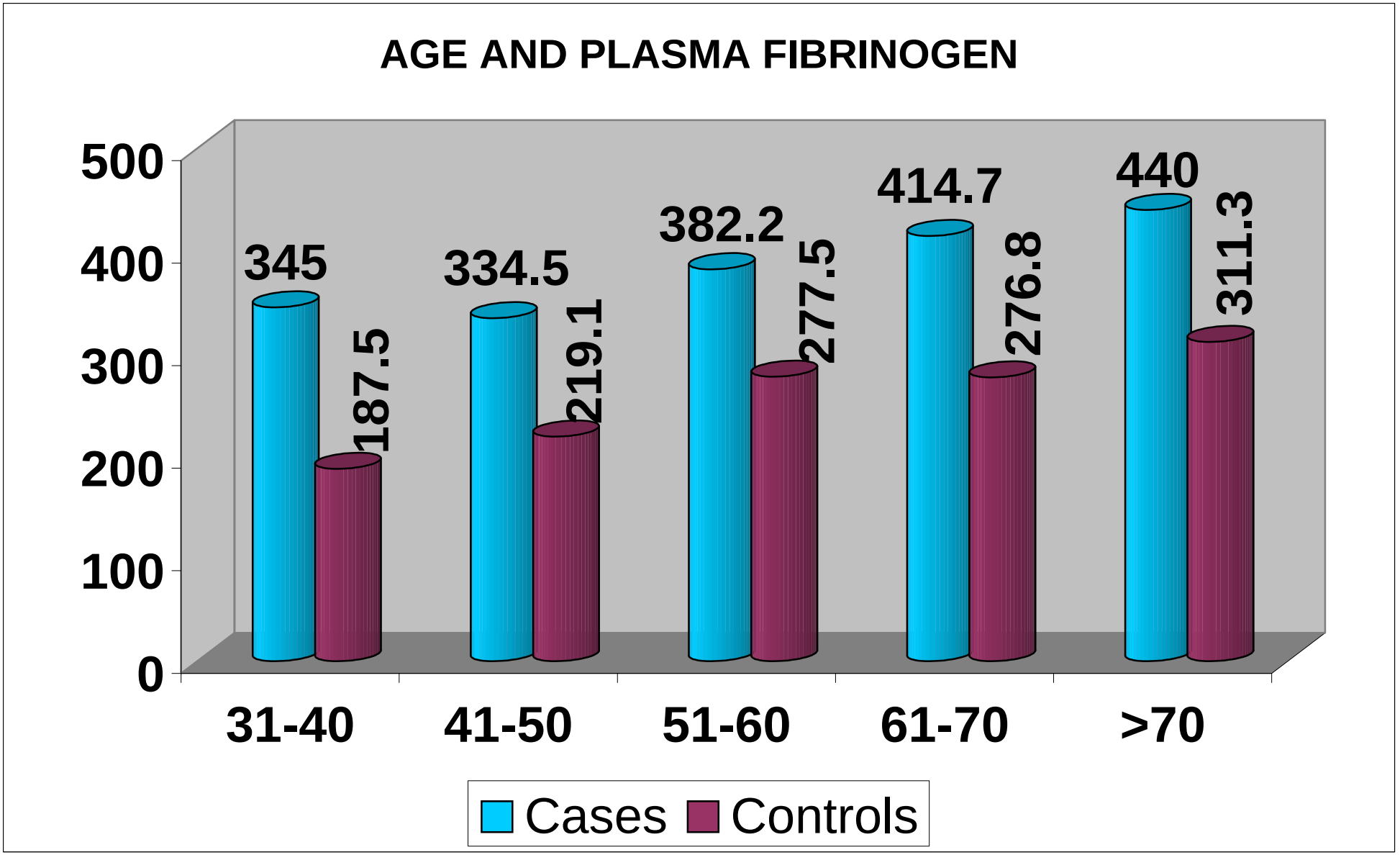
MEAN PLASMA FIBRINOGEN IN CASES Vs CONTROLS

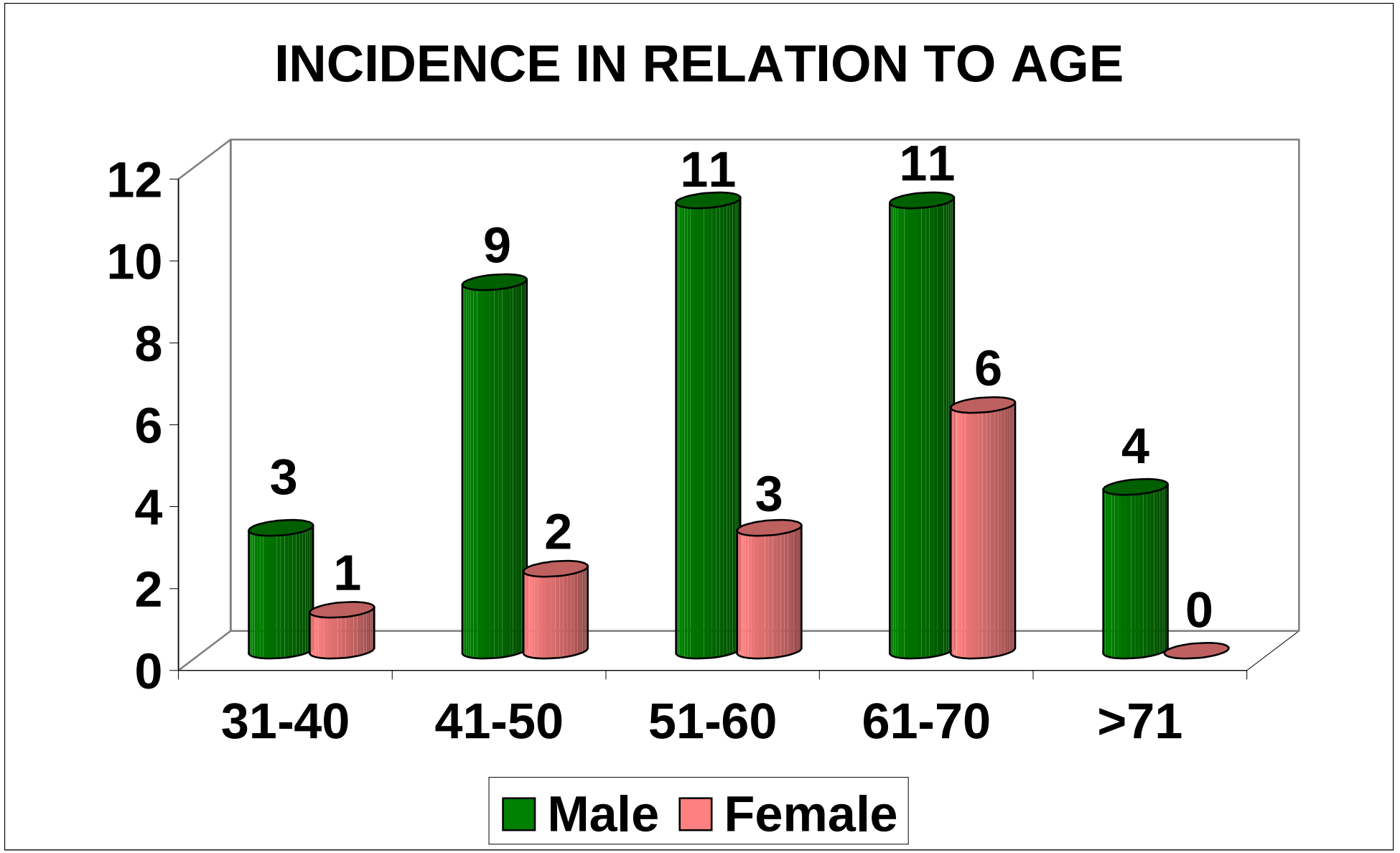



HT AND PLASMA FIBRINOGEN
431.3
355.7
300.6
239.1
450
400
350
300
250
200
150
100
50
0
Cases
Controls
HT
Non HT


DM AND PLASMA FIBRINOGEN
600
450
300
150
0
435.5
307.8
320.5
212.5
Cases
Controls
Diabetes
Non Diabetes

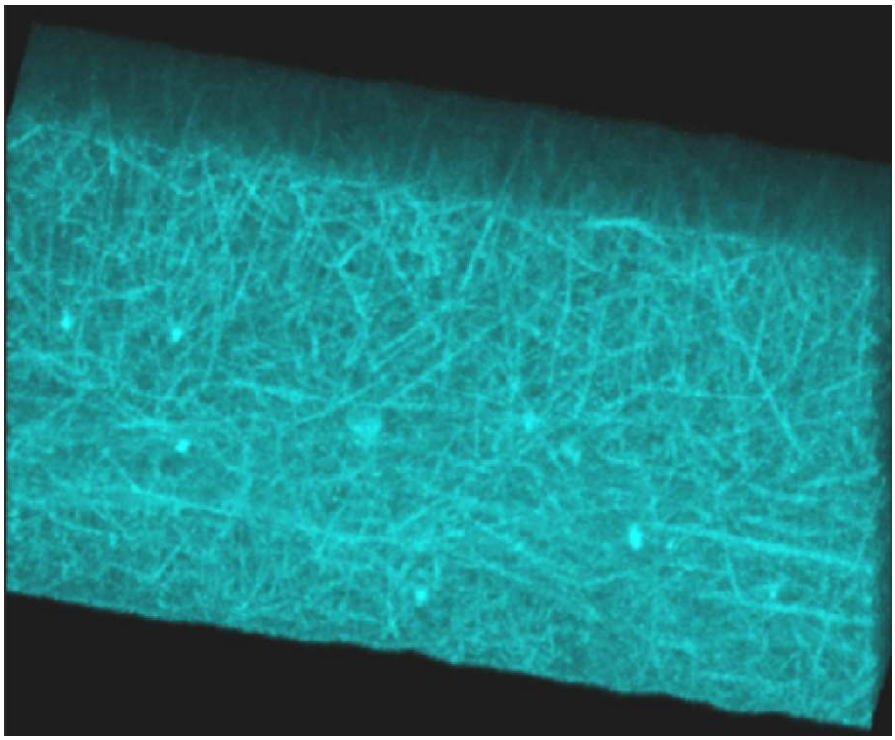

SEX AND PLASMA FIBRINOGEN
500
400
300
200
100
0
384.5
384.2
275
210
Cases
Controls
Male
Female

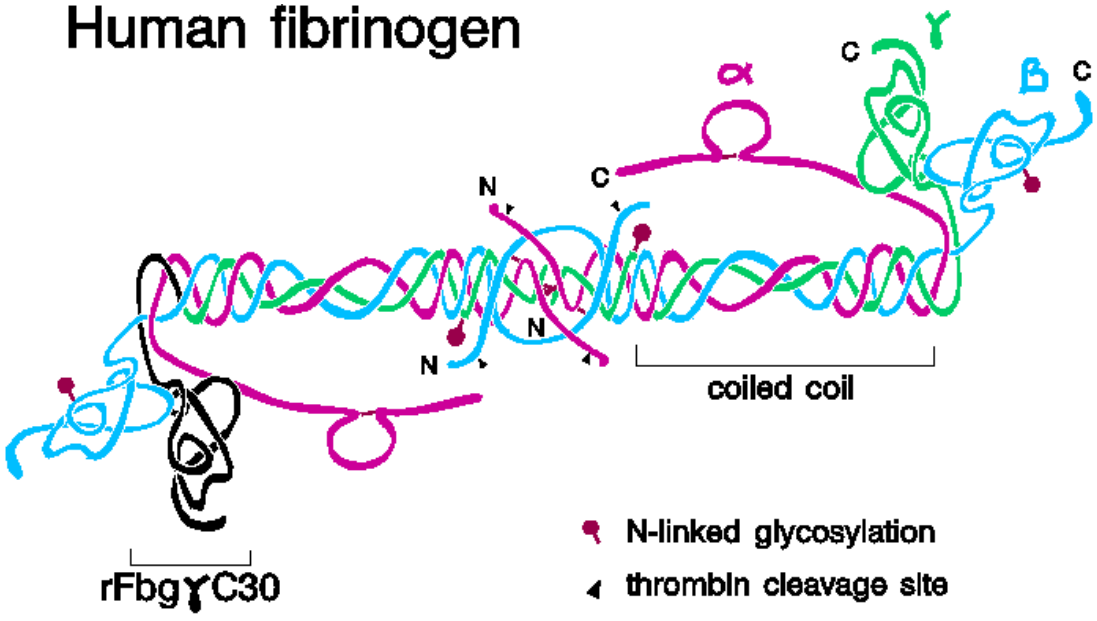

AGE AND PLASMA FIBRINOGEN
500
400
300
200
100
0
345
187.5
334.5
219.1
382.2
277.5
414.7
276.8
440
311.3
31-40
41-50
51-60
61-70
>70
Cases
Controls


INCIDENCE IN RELATION TO AGE
12
10
8
6
4
2
0
3
1
9
2
11
3
11
6
4
0
31-40
41-50
51-60
61-70
>71
Male
Female

CT PICTURE OF INFARCTION

ELECTRON MICROSCOPIC PICTURE PLASMA FIBRINOGEN





(H. Cote, adapted from R. F. Doolittle)

THE CIRCLE OF WILLIS

The circle of willis